FORMULATION AND EVALUATION OF DOMPERIDONE MICROPARTICLES

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

V.MURUGAIYAN

(Reg. No: 261511151)

Under the guidance of

Prof., **K.Shahul Hameed Maraicar,** M.Pharm., (Ph.D).,

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF DOMPERIDONE MICROPARTICLES "** submitted by **V.MURUGAIYAN** (Reg. No: 261511151) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S Pillay College of Pharmacy during the academic year 2016-2017.

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1.INTRODUCTION

Microparticles are solid, approximately spherical particles ranging 1-1000 micrometers in size. They are made up of polymeric substances, in which the drug is dispersed throughout the microparticles matrix. Microparticles are sometimes referred to as micro particles and other synonymous words are micro beads, beads and microspheres.

Microparticles are small particles that contain an active agent or core material surrounded by a shell or coating of polymers. The core can be solid, liquid, or gas. The shell is a continuous, porous or nonporous, polymeric layer. Microparticles show different release properties compared to true microparticles and an additional feature is that catastrophic drug burst due to rupture of the shell cannot occur[1].

Necessity of using Microparticles:

The conventional drug delivery systems in use, in many cases fail to meet the need of efficient drug delivery at the target site/organ and thereby elicit a less efficacious pharmacological response with several side effects. However, advances in microparticles have filled this gap to a large extent because of following advantages.

Formulation of Microparticles:

The preparation of microparticles includes usage of both natural and synthetic polymers. The formulation of Microparticles consists of polymers of bio-degradable and non- biodegradable type, as carriers materials.

Types of polymers:

- Synthetic Polymers
- Natural polymers

SYNTHETIC POLYMERS:

a) **Non-biodegradable polymers:**

Poly methyl methacrylate(PMMA), Acrolein, Glycidyl methacrylate, Epoxypolymers

b) **Biodegradable polymers:**

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

NATURAL POLYMERS:

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, Collagen, Pectin, Guar Gum, Xanthun gum.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Poly dextran**,** Poly starch.

METHODS OF PREPARATION:

- ✓ Emulsion solvent evaporation technique
- ✓ Emulsion cross linking method
- ✓ Coacervation method
- ✓ Spray drying technique
- ✓ Emulsion-solvent diffusion technique
- ✓ Multiple emulsion method
- ✓ Ionic gelation

EMULSION SOLVENT EVAPORATION TECHNIQUE:

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microparticles by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs. Aceclofenac microparticles were prepared by this technique[5].

EMULSION CROSS LINKING METHOD:

In this method drug was dissolved in aqueous gelation solution which was previously heated for 1 hr at 40^{o}C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35^{o}C, results in w/o emulsion then further stirring is done for 10 min at 15^{o}C.

Thus the produced microparticles were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glycine solution containing 0.1%w/v of tween 80 at 37^{o}C for 10 min to block un reacted glutaraldehyde.

COACERVATION METHOD:

Coacervation thermal change, performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80^{o}C by heating. Then the drug was finely pulverized and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through sieve (sieve no. 40) to obtain individual microcapsule.

Coacervation non solvent addition, developed by weighed amount of ethyl cellulose was dissolved in toluene containing propyl-isobutylene in closed beaker with magnetic stirring for 6 hr at 500 rpm and the drug is dispersed in it and stirring is continued for 15mins. Then phase separation is done by petroleum benzoin with continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hr and then in oven at 50^{o}C for 4 hr.

SPRAY DRYING TECHNIQUE:

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent.

Organic solution of poly (epsilon caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microparticles. This is rapid but may loose crystalinity due to fast drying process.

EMULSION-SOLVENT DIFFUSION TECHNIQUE:

In order to improve the residence time in colon floating microparticles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microparticles were washed and dried in a dessicator at room temperature. The following microparticles were sieved and collected.

MULTIPLE EMULSION METHOD:

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then re-emulsified in aqueous medium. Under optimized condition discrete microparticles were formed during this phase.

IONIC GELATION:

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca2+ /Al3+ and chitosan solution in acetic acid.

Microparticles which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH.4-7.2 but the drug did not release in acidic pH.

Advantages of Microparticles:

- They facilitate accurate delivery of small quantities of potent drugs and reduced concentration of the drug at sites other than the target organ or tissue.
- They provide protection for unstable drugs before and after administration, prior to their availability at the site of action.
- They provide the ability to manipulate the *invivo* action of the drug, pharmacokinetic profile, tissue distribution and cellular interactions of the drug.
- They enable controlled release of the drug.

Sometimes, in formulation of microparticles, cross-linking agents are added. The role of cross-linking agent is as follows:

Cross-links: These are bonds that link one polymer chain to another. They can be covalent bonds or ionic bonds. Polymer chains can refer to synthetic polymers or natural polymers (such as proteins). When the term "cross-linking" is used in the synthetic polymer science field it usually refers to the use of cross-links to promote a difference in the polymers physical properties[2].

When polymer chains are linked together by cross-links, they lose some of their ability to move as individual polymer chains. For example, a liquid polymer (where the chains are freely flowing) can be turned into a solid or gel by cross-linking the chains together.

In polymer chemistry, when a synthetic polymer is said to be cross-linked, it usually means that the entire bulk of the polymer has been exposed to the cross-linking method. The resulting modification of mechanical properties depends strongly on the cross-link density. Low cross-link densities raise the viscosities of polymer.

Intermediate cross-link densities transform gummy polymers into materials that have elastomeric properties and potentially high strengths. Very high cross-link densities can cause materials to become very rigid or glassy, such as phenol-formaldehyde materials.

Cross linking Agents:

Cross-links can be formed by chemical reactions that are initiated by heat, pressure, change in pH, or radiation. For example, mixing of an unpolymerized or partially polymerized resin with specific chemicals called cross linking reagents that result in a chemical reaction that forms cross-links.

Examples: Imidoester crosslinker dimethyl suberimidate, the NHS-ester cross linker BS3 and formaldehyde, glutaraldehyde, vinylsilane etc.

Each of these cross linkers induces nucleophilic attack of the amino group of lysine and subsequent covalent bonding via the cross linker. The zero-length carbodiimide cross linker EDC functions by converting carboxyl into amine-reactive iso-urea intermediates that bind to lysine residues or other available primary amines. SMCC or its water soluble analog, Sulfo-SMCC, are commonly used to prepare antibody-hapten conjugates for antibody development.

Drug Release Kinetics:

Release of the active constituent is an important consideration in case of Microparticles. The release profile from the Microparticles depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable. The drugs could be released through the Microparticles by any on the three methods[4].

- Osmotically driven burst mechanism
- Pore diffusion method.
- Erosion or degradation of the polymer.

Burst mechanism:

In this, water diffuses into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst mechanism is mainly affected by 3 factors namely macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the Microparticles.

Pore diffusion method:

It is named so because as penetrating waterfront continue to diffuse towards the core. The dispersed protein/drug dissolves creating a water filled pore network through which the active principles diffuses out in a controlled manner.

Polymer erosion:

Loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix finally leads to the cleavage of the hydrolytic bonds. The cleavage of the bond is also facilitated by the presence of the enzyme in the surroundings. The erosion of the polymer may either surfacial or it may be bulk leading to the rapid release of water uptake therefore determines release profile of the system and depends on type of the polymer, porosity of the polymer matrix, protein drug loading[3].

Drug Release from the swellable polymer:

The entry of water into the polymer matrix followed by swelling and gelation and then diffusion of drug through the viscous gel occurs when water-soluble matrices (hydrophilic matrices) are used.

Factors affecting the release of the drug from the particulate system in relation to drug, microparticles bio-environment:

Drug

- Position in microparticles
- Molecular weight
- Physicochemical properties
- Concentration
- Interaction with matrix

Microparticles

- Type and amount of the matrix polymer
- Size and density of the Microparticles
- Extent of cross linking, denaturation or polymerization.
- Adjuvants

Environment

- pH
- Polarity
- Presence of enzyme

Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.

Reservoir system*:*

Release from the reservoir type system with rate controlling membrane proceeds by first penetration of the water through the membrane followed by dissolution of the drug in the penetrating dissolution fluid. The dissolved drug, after partitioning moves through the membrane across the stagnant diffusion layer[6].

The release is essentially governed by the Fick's First law of Diffusion as

$$J = -D(dc/dx)$$

Where, J= flux per unit area

D = Diffusion coefficient

dc/dx = concentration gradient.

Matrix system:

Release profile of the drug from the matrix type of the device critically depends on the state of drug whether it is dissolved or dispersed in the polymer matrix. In case of the drug dissolved in the polymeric matrix, amount of drug and the nature of the polymer[10].

APPLICATION OF MICROPARTICLES

Microparticles in Vaccine Delivery:

The prerequisite of a vaccine is protection against the microorganism of its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and minimization of adverse reaction is a complex issue. The aspect of safety and the degree of production of antibody responses are closely related to mode of application. The interest in parenteral carrier lies since they offer specific advantages including:

- Improved antigenicity by adjuvant action
- Modulation of antigen release.
- Stabilization of antigen.

Polymers used for Vaccine Delivery system:

Biodegradable polymers belong to a class of choice for the delivery of the vaccine since they do not require surgical removal.

Examples are PLGA polylactic acid, polyglycolic polymers etc.

Stability of Microparticles in vaccine delivery*:*

Antigen polymer compatibility is a major barrier encountered in the design of a suitable carrier because it may lead to the stability problem. The polymer compatibility can be increased by co-encapsulating buffer salts and stabilizers for proteins which are thought to increase antigen stability by modifying the internal pH of Microparticles and accelerating swelling[7].

The use of tri-block copolymers having hydrophilic A block (PLGA or PLA) and hydrophilic B block (polyoxyethylene, PEO) also provide stability to the carrier system by providing more gentle and an accommodative system.

Microparticles in Immune system:

The interaction of the Microparticles with macrophages depends upon the particle size. Microparticles of particle size less than 10micrometers are directly taken up by the antigen presenting cells. The microparticles with particle size range greater than 10 micrometers first undergo degradation or release of antigens, which are then phagocytosized by antigen presenting cells. The antigen presenting cells are responsible for the activation of bad T cells and hence immunological consequences.

Monoclonal Antibodies mediated Microparticles Targeting Immune:

Monoclonal antibodies mediated targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of the monoclonal antibodies can by utilize to target Microparticles loaded bioactive molecules to selected sites.

Mabs can be directly attached to the Microparticles by means of covalent coupling. The free aldehyde groups, amino groups, or hydroxyl groups on the surface of the Microparticles can be linked to the antibodies.

Microparticles from different material and prepared using different methods carry different functional groups, which help in the coupling of the antibodies.

The mabs can be attached to the Microparticles by any of the following methods:

- Non-specific adsorption
- Specific adsorption
- Direct Coupling
- Coupling via reagents.

Non-specific adsorption:

Mabs can be adsorbed nonspecifically on to the surface of the hydrophobic microparticles by physical adsorption, which renders them more hydrophilic. Hydrophilic microparticles are more suitable for the cell targeting. Monoclonal antibodies form immune-microparticles on coupling with the microparticles[9].

Specific adsorption:

It can be conducted by means of the ligands, which interact directly with intact or modified antibodies. Proteins A from Staphylococcus aurueus and avidin biotin are two specific ligands that are used for specific adsorption purpose.

Direct coupling: It is achieved through free functional groups present on the surface of the microparticles. The functional Microparticles undergo direct coupling, e.g. polyacrolien microparticles have free functional carboxyl groups, which help them to couple with the monoclonal antibodies.

Coupling via reagents:

Coupling of Microparticles with monoclonal antibodies can also be achieved by means of the reagents when Microparticles of choice do not contain functional groups or carry functional groups, which are not capable of coupling. Different methods depending on the reagent used include carbodimide method and cyanogens bromide method.

Cancer chemotherapy:

Microparticles are used mainly in targeting the tumorous organ. In this, the Microparticles are directly administered to the tumorous organ by means of local intra-arterial injection.

Disadvantages of Microparticles:

The main disadvantages of Microparticles are as follows:

- The phagocytosis of colloidal carriers
- Rapid clearance
- Passive distribution

The change in the biophysical behavior of the particles helps to avoid the difficulties in targeting. Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution pattern.

Surface Modifiers:

They modify the surface properties of carriers in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body. Among the most studied surface modifiers are

1. Antibodies and their fragments.
2. Proteins.
3. Mono, oligo and polysaccharides.
4. Chelating compounds such as EDTA, DTPA or Desferroxamine
5. Synthetic soluble polymers.

The surface of the albumin Microparticles can be modified by covalent attachment of polyoxy alkyene chain having terminal ether groups. The polyoxyethylene moiety may react with surface amino or carboxyl residues by condensation with an appropriate functional group in the presence of the condensing agent[8].

Stability and storage:

The Microparticles formulations are stored at 25± 2ºC and 60 ± 5% RH for a period of 6 months and at 5± 3º C for a period of 12 months, which is the accelerated storage temperature and long-term storage temperature, respectively, for products intended to be refrigerated. The decision to refrigerate was taken because of the thermo-sensitivity and thermo-liability of the polymers chosen. The stored samples are tested for their drug content, particle size distribution and for any physical change.

2.AIM AND OBJECTIVE

The present work is carried out to formulate and evaluate the Domperidone microparticles by ionic gelation technique by using natural polymers. Domperidone is an anti-dopaminergic drug agent that is used orally, rectally or intravenously, in general to suppress nausea and vomiting. It is a specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis and is used as antiemetic

The aim of the preparation is to improve the drug-polymer encapsulating capacity of the microparticles. So that the microparticles with desired controlled release features are obtained. There are many methods to achieve controlled release of drug from the dosage form. Among them, ionic gelation method is one. This method, that is, gel forming ability is simple way of obtaining particulate drug carriers.

Studies using natural polymers guar gum, pectin, xanthun gum besides synthetic ones such as PLGA, have been carried out. The entrapment efficiency of the microparticles is affected by drug and polymer ratio. The domperidone microparticles were prepared by using natural polymers, so as to obtain the controlled release of drug from the formulation.

Natural polymers are known to form reticulated structures, when in contact with calcium ions and their characteristics have been used to produce sustained release particulate systems for a variety of drugs. Domperidone has been selected as a model drug because it helps to move food faster through food pipe, stomach, gut and does not stay in the same place too long providing the required action of emetic.

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3.PLAN OF WORK

The study was proposed to carry out in the following studies:

1. **Preformulation Studies**

    1. Compatibility studies.
    2. Fourier transform infrared spectroscopy (FTIR)

2. **Preparation of Standard Calibration Curve for Domperidone**

3. **Formulation of Microparticles of Domperidone**

4. **Evaluation of Prepared Microparticles**

    - Swelling Studies
    - Entrapment Studies
    - *In vitro* Dissolution Studies.
    - Drug Release Kinetics
    - Particle size

4.LITERATURE SURVEY

Park H J et al.[11] Chitosan microparticles were prepared with tripolyphosphate (TPP) by ionic cross linking. The particle sizes of TPP chitosan microparticles were in range from 500 to 710 mm and encapsulation efficiencies of drug were more than 90%. The morphologies of TPP-chitosan microparticles were examined with scanning electron microscopy. As pH of TPP solution decreased and molecular weight (MW) of chitosan increased, microparticles had more spherical shape and smooth surface. Release behaviors of felodipine as a model drug were affected by various preparation processes. Chitosan microparticles prepared with lower pH or higher concentration of TPP solution resulted in slower felodipine release from microparticles. With decreasing MW and concentration of chitosan solution, release behavior was increased. The release of drug from TPP-chitosan microparticles decreased when cross-linking time increased. These results indicate that TPP-chitosan microparticles may become a potential delivery system to control the release of drug.

Paolo Blasi et al.[12] The aim of this work was to develop a novel composite alginate/poly (lactic-co-glycolic) acid microparticulate system for protein stabilization and delivery using bovine insulin as model drug. Alginate particles, prepared by ionic gelation, were embedded into PLGA microparticles using the solvent diffusion evaporation technique. Actual loading was determined by micro-BCA protein assay for total insulin and by reversed phase-high performance liquid chromatography for soluble insulin. Insulin loaded composite microparticles showed reproducible encapsulation efficiency with a higher soluble insulin content when compared to conventional microparticles. Bovine insulin *in vitro* release studies and adsorption behavior were investigated in 10mM glycine buffer (pH 2.8) at 37 ◦C. The stability of bovine insulin, olubilized in the above mentioned buffer, was studied as well.

In this case, bovine insulin showed to be instable at the investigated conditions and 55% of insulin was lost after 7days. However, composite microparticle release, characterized by a low burst effect, lasted up to 4 months. Moreover, no significant peptide adsorption on blank PLGA or blank composite microparticles was observed while, a strong interaction between alginate particles and bovine insulin was detected.

Bataille B et al.[13] Experimental factorial designs were built to investigate the effects of five parameters on production yields and moisture contents of spray-dried products. These factors concerned both the solution feed (drug concentration, colloidal silica concentration and polymer: drug ratio) and the spray dryer (inlet temperature and feed rate). Three formulations containing cellulose derivatives and acetaminophen were tested. The aim of the study was to optimize the operating conditions to maximize production yields while minimizing moisture contents. First screening experiments consisting of fractional factorial designs revealed the most significant factors to be inlet temperature, feed rate and their interaction for both formulations containing sodium carboxymethyl cellulose and feed rate and colloidal silica concentration for the formulation containing microcrystalline cellulose.

Then, the optimal operating conditions were estimated by response surface methodology. Central rotational composite designs showed quadratic models were adequate. New assays were carried out using these last conditions to evaluate both the repeatability and reproducibility of the spray-drying technique. Yields above 80% and moisture content of _1% were reached. The characterization of microparticles revealed the poor flow ability of the spray-dried products due to significant cohesiveness and very small size (less than 55 mm).

Tetsuya Ozeki et al.[14] In this study, we used a novel 4-fluid nozzle spray drier to prepare composite microparticles of a water-insoluble drug, flurbiprofen (FP), and a water-soluble drug, sodium salicylate (SS), for the purpose of improving the water solubility of FP. An ethanol solution of FP and an aqueous SS solution were simultaneously introduced through different liquid passages in the 4-fluid nozzle spray drier and then spray-dried. Quantitative elemental analysis suggested that the FP/SS ratio in each composite microparticle was nearly the same as the formulation ratio. We also found that SS and FP exist in a low crystalline state in the composite particles. Release of FP from dissolved composite microparticles was markedly improved because of an increase in the effective surface area following rapid dissolution of SS. This study shows that it is possible to prepare FP–SS composite microparticles using a 4-fluid nozzle spray drier in single process and that this can improve the ability of FP to dissolve in water.

Yuuki Takashima et al.[15] Preparation of nano-sized particles using lyophilization, which is a standard drying technique for high-molecular-weight compounds such as bioactive peptides, proteins, plasmid DNA and sRNA, often results in particle aggregation. In this study, spray-drying was applied for preparation of cationic PLGA nanospheres as gene delivery vectors in order to minimize aggregation and loss of gene transfection efficiency. PLGA nanoparticles emulsions were prepared by dropping an acetone/methanol mixture (2/1) containing PLGA and a cationic material, such as PEI, DOTMA, DCChol or CTAB, into distilled water with constant stirring. The PLGA nanosphere emulsion was dried with mannitol by spray-drying, and mannitol microparticles containing PLGA nanosphere were obtained.

Mean particle diameter of spray dried PLGA particles was 100–250 nm, which was similar to that of the nano-emulsion before drying, whereas the lyophilized PLGA particles showed increased particle diameter due to particle aggregation. PEI, DOTMA and DC-Chol were useful for maintaining nanoparticles size and conferring positive charge to nanosphere. Transfection of pDNA (pCMV-Luc) using these spray-dried cationic PLGA nanosphere yielded high luciferase activity in COS-7 cells, particularly with PLGA/PEI nanosphere. The present spray-drying technique is able to provide cationic PLGA nanosphere, and may improve redispersal and handling properties

Artusi M et al.[16] This study investigated the possibility to use spray drying technique to prepare powders formulations containing caffeine intended for nasal delivery. Spray dried powders containing caffeine and excipients, as filler and shaper agents, were prepared. Powders were investigated for particle size, morphology and delivery properties from Monopowder P® nasal insufflators, assessing the influence of each excipient on microparticles characteristics. The results showed that the excipients strongly affected microparticle properties. Size, shape and agglomeration tendency are relevant characteristics of spray dried nasal powder.

Rita Cortesi et al.[17] The aim of the present paper was to study production of methacrylate microparticles for the delivery (administration) of ascorbic acid via the oral route. Vitamin C is an important antioxidant that may be involved in the reduction of the risk of certain types of cancer, such as colorectal cancer. As polymers different acrylic compounds were considered, namely Eudragit® RL, L and RS. Spray-drying was used as preparation method of vitamin C/Eudragit® microspheres.

Microspheres were first characterized by size and morphology by scanning electron microscopy, then in vitro release kinetics by mean of dialysis method were studied. Although the produced microparticles were unable to slow down the release of the drug with respect to the free form of ascorbic acid, these microspheres showed a good morphology and size distribution that permit to propose them as candidate for the delivery of vitamin C as associated therapy in the treatment of colorectal cancer by oral route.

Yogesh Pore et al.[18] Abstract The aim of the present study was to enhance the physicochemical properties of poorly aqueous soluble Carvedilol (CRV) by preparing its microparticles in presence and/or in absence of a hydrophilic carrier. The polymeric microparticles of CRV were prepared with polyvinylpyrrolidone K30 with or without addition of adsorbents like Aerosil_200 and/or Sylysia_350 by using spray drying technique. The dissolution profiles revealed that the drug and polymer ratio and colloidal silica both played critical role in solubility enhancement. The spray dried microparticles and drug alone were characterized by differential scanning calorimetry (DSC), X-ray powder diffraction, Fourier transformation infrared spectroscopy (FTIR), particle size analysis and scanning electron microscopy (SEM). DSC analysis showed that CRV transformed from the crystalline state to amorphous state by spray drying, confirmed by disappearance of its melting peak. The results of the X-ray analysis were in agreement with the thermal analysis data. It did not show characteristic crystalline drug peaks which confirmed that the amorphous form of CRV was present in the CRV loaded microparticles. FTIR analysis demonstrated hydrogen bonding interaction with an absence of significant chemical interaction between CRV and polymer. Spherical microparticles were yielded with smooth surfaces as observed by SEM. All in all, this work reveals that spray drying is a suitable technique for preparation of microparticles with improved physicochemical properties of CRV.

Diego A. Chiappetta et al.[19] The aim of this work was to develop indinavir pediatric anti-HIV/AIDS formulations enabling convenient dose adjustment, ease of oral administration, and improved organoleptic properties by means of the generation of drug-loaded microparticles made of a polymer that is insoluble under intake conditions and dissolves fast in the stomach in order to completely release the active agent. Indinavir loaded microparticles made of a pH-dependent polymeric excipients soluble at pH<5, Eudragit E100, were prepared using a double emulsion solvent diffusion technique and the in vitro release profiles characterized. Finally, taste masking properties were evaluated in blind randomized sensory experiments by ten healthy human volunteers. The use of a w/o/o emulsion system resulted in indinavir loads around 90%. Thermal analysis of the microparticles by differential scanning calorimetry revealed that indinavir appeared mainly dispersed at the molecular level. Concentrations of residual organic solvents as determined by gas chromatography were below the upper limits specified by the European Pharmacopeia for pharmaceutical oral formulations. Then, the behavior of drug-containing microparticles in aqueous media at different pH values was assessed. While they selectively dissolved in gastric like medium, in tap water (intake conditions), the matrix remained almost unchanged and efficiently prevented drug dissolution. Finally, sensoring taste tests performed by volunteers indicated that systems with indinavir loads 15% displayed acceptable taste. This work explored the production of indinavir containing microparticles based on a common pharmaceutical excipients as a means for the improvement of medicines of drugs involved in the treatment of HIV/AIDS. For systems containing about 15% drug, taste studies confirmed the acceptability of the formulation. In pediatric regimes, this composition would require an acceptable amount of formulation (0.7–1.5 g).

Perumal D et al.[20] The emulsion solvent diffusion was employed to prepare modified release microspheres of ibuprofen. The technique was optimized for the following processing variables: the absence/presence of baffles in the reaction vessel, agitation rate and drying time. Thereafter, the influence of various formulation factors on the microencapsulation efficiency, in vitro drug release and micromeritic properties was examined. The variables included the methacrylic polymer, Eudragit® RS 100, ibuprofen

content and the volume of ethanol used during microencapsulation. The results obtained were then interpreted on a triangular phase diagram to map the region of microencapsulation, as well as those formulations that yielded suitable modified release ibuprofen microspheres.

Rajesh Kaza et al.[21] The purpose of this study was to prepare controlled release microspheres of acyclovir sodium using different polymers like sodium alginate, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose using calcium chloride as cross linking agent. The microspheres were prepared using ionotropic gelation technique. The prepared microspheres were evaluated for particle size analysis, drug entrapment efficiency; *In vitro* drug release and Fourier transform infra red spectroscopy (FTIR). The results of study revealed that retention time of acyclovir at its absorption site could be increased by formulating it into microspheres using sodium alginate, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose in different ratios. The acyclovir sodium microspheres prepared from sodium alginate and hydroxyl propyl methyl cellulose at the concentrations of 1:2:1.5 weight ratios with 2% calcium chloride as cross linking agent showed the highest drug release of 98.8 % over a period of 12 hours. The microspheres prepared were found to be spherical without aggregation and free flowing. The percentage yield and drug entrapment in all the formulations were good. The average particle size was found to be within the range of 100-200 micrometers.

All the formulations show excellent flow ability as expressed in terms of angle of repose (< 25°).FTIR Spectroscopy reveals that there is no chemical interaction between the drug and excipients.

Chintagunta Pavanveena et al.[22] Trimetazidine hydrochloride-loaded Gelatin microspheres were prepared by the ionic cross-linking technique using TPP as cross-linking agent. The process induced the formation of microspheres with the incorporation efficiency of 47% to 77%. The effect of Gelatin concentration, cross-linking agents and conditions was evaluated with respect to entrapment efficiency, particle size, surface characteristics and *in vitro* release behaviors. Infrared spectroscopic study confirmed the absence of any drug-polymer interaction. Differential scanning colorimetric analysis revealed that the drug was molecularly dispersed in the Gelatin microspheres matrices showing rough surface, which was confirmed by scanning electron microscopy study. The mean particle size and entrapment efficiency were

found to be varied by changing various formulation parameters. The *in vitro* release profile could be altered significantly by changing various formulation parameters to give a sustained release of drug from the microspheres. The kinetic modeling of the release data indicate that trimetazidine hydrochloride release from the Gelatin microspheres follow anomalous transport mechanism after an initial lag period when the drug release mechanism was found to be fickian diffusion controlled.

Akanksha Garud et al.[23] The purpose of the present study was to prepare, characterize and evaluate the colon-targeted microspheres of mesalamine for the treatment and management of ulcerative colitis (UC). Microspheres were prepared by the ionic-gelation emulsification method using tripolyphosphate (TPP) as cross linking agent.

The microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach. The prepared microspheres were evaluated for surface morphology, entrapment efficiency, drug loading, micromeritic properties and in-vitro drug release. The microspheres formed had rough surface as observed in scanning electron microscopy. The entrapment efficiency of microspheres ranged from 43.72%-82.27%, drug loading from 20.28%-33.26%. The size of the prepared microspheres ranged between 61.22-90.41μm which was found to increase with increase in polymer concentration. All values are statistically significant as $p<0.05$. Micromeritic properties showed good flow properties and packability of prepared microspheres. The drug release of mesalamine from microspheres was found to decrease as the polymer concentration increases. The release profile of mesalamine from eudragit-coated chitosan micro-spheres was found to be pH dependent. It was observed that Eudragit S100 coated chitosan microspheres gave no release in the simulated gastric fluid, negligible release in the simulated intestinal fluid and maximum release in the colonic environment. It was concluded from the study that Eudragit-coated chitosan microspheres were promising carriers for colon-targeted delivery of Mesalamine.

Canefe et al.[24] Indomethacin-loaded microspheres of ethylcellulose were prepared by the emulsion solvent evaporation technique. The aim of this work was to investigate the influence of process variation in polymer type via viscosity grades of ethylcellulose N10 and N100, drug to polymer ratio, stirring rate of the propeller and surfactant type on the micromeritic properties of microspheres such as

particle size distribution, bulk and tapped density, surface topography, tangent of angle of repose, compressibility index, Hausner ratio and flow rates.

All microspheres presented a narrow particle size distribution and good flow characters according to USP 28-NF 23 criteria, besides microspheres were more spherical in shape in their manufacture with ethylcellulose N100 and higher ratio of both polymers. Thus, in the case of ethylcellulose, the viscosity and ratio of the polymer in dispersion medium were found to be the controlling factors of drug release. Ethylcellulose N10 and N100 membrane materials indicated difference in release patterns of microspheres. Microspheres exhibited lower burst effect with decreased drug release rate, when the drug was incorporated with ethylcellulose N100 and higher ratio of each polymer. Therefore, Indomethacin release from ethylcellulose microspheres could not be evaluated by any of the kinetic models.

Basu S K et al.[25] The aim of the work was to prepare nitrendipne-loaded Eudragit RL 100 microspheres to achieve sustained release nitrendipine. Nitrendipne-loaded Eudragit RL 100 microspheres were prepared by an emulsion-solvent evaporation method using ethanol/liquid paraffin system. The resultant microspheres were evaluated for average particle size, drug loading, in vitro drug release and release kinetics. FTIR spectrometry, scanning electron microscopy, differential scanning calorimetry and x-ray powder diffractometry were used to investigate the physical state of the drug in the microspheres. The mean particle size of the microspheres was influenced by varying drug: polymer ratio and emulsifier concentration while drug loading was dependent on drug: polymer ratio. The results of FTIR spectrometry, differential scanning calorimetry and x-ray diffractometry indicated the stable character of nitrendipne in drug-loaded microspheres and also revealed absence of drug-polymer interaction. The drug release profiles of the microspheres at pH 1.2 showed poor drug release characteristics while at pH 6.8,drug release was extended over a period of 8 hr release was influenced by polymer concentration and particle size. Drug release followed the Higuchi model.

The nitrendipine-loaded Eudragit RL 100 microspheres prepared under optimized conditions showed a good sustained release characteristic and were stable under the conditions studied.

Himansu Bhusan Samal et al.[26] The present study involves design and characterization of floating microspheres with Nateglinide as model drug for prolongation of gastric residence time. Nateglinide Floating Microspheres were prepared by **w/o/o** emulsification solvent diffusion technique using rate controlling polymers ethyl cellulose and hydroxy propyl methyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy respectively. FTIR analyses the absences of drug-polymer interaction. In vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of polymer concentration, solvent composition, particle size, drug entrapment efficiency and drug release were also observed. The prepared microspheres exhibited prolonged drug release (more than 12 h) and remained buoyant for > 24 hr. The mean particle size increased and the drug release rate decreased at higher polymer concentration. In vitro studies demonstrated diffusion- controlled drug release from the microspheres.

Namdeo k p et al.[27] In the present study, spherical microspheres of theophylline (TP) using sodium alginate as the hydrophilic carrier were prepared to prolong the release. The shape, surface and size characteristics were determined by scanning electron microscopy. The microspheres were found to be discreet and spherical in shape and had a smoother surface. The mean diameter of seven alginate microspheres formulations were between 7.6 ± 0.52 and 22.35 ±0.31 μm. It was observed that mean particle size of the microspheres increased with an increase in the concentration of polymer.

The entrapment efficiency was found to be in the range of 70–93%. Optimized alginate microspheres were found to possess good sphericity, size and adequate entrapment efficiency. The in vitro release studies were carried out in pH progression media. Results indicated that percent drug release decreased with an increased alginate concentration. TP-loaded Alginate microspheres showed extended in vitro drug release thus use of microspheres potentially offers sustained release profile along with improved delivery of TP.

Nazia Khanam et al.[28] The aim of present research work was to formulate and evaluate microspheres of Propranolol Hydrochloride to achieve sustained release system using combination of algino-eudragit RS100 system by ionic-gelation technique. The prepared microspheres were evaluated for various parameters like percentage yield, particle size, flow property, entrapment efficiency, surface study, in-vitro drug release, X-Ray diffraction analysis, etc. It was found that all formulations showed improved flow behavior as compared to pure drug, it was observed that on increasing the polymer concentration of formulations the entrapment efficiency and particle size were increased. The surface morphology study by SEM indicated that microspheres were spherical with rough outer surface. There was no interaction between the drug and the polymers, as studied by FTIR study. In-vitro drug release study showed that on microsphere formulation its release was sustained and its release was affected by polymer concentration and it followed Higuchi model. Therefore, it can be concluded that Propranolol Hydrochloride loaded algino-eudragit RS100 microspheres can be formulated for sustained drug delivery of Propranolol Hydrochloride

Rohit B Mane et al.[29] The aim of this study was to preparation and evaluation of Carvedilol microsphere using spray drying technique and to optimize the spray drying parameters to get the optimum formulation. The Carvedilol microsphere were prepared by spray drying technique using ethyl cellulose and PEG 6000 as sustained release polymers. Nine batches were prepared by using ethyl cellulose and PEG 6000 in different polymer ratios and prepared microspheres were evaluated for the particle size, percentage drug entrapment and percentage drug release. Experimental designs were built to investigate the effects of five parameters on production yields and particle size of spray-dried microspheres of Carvedilol. These factors concerned aspiration speed, flow rate, drug polymer ratio, temperature difference between inlet temperature and outlet temperature. Three formulations containing ethyl cellulose, PEG 6000 and Carvedilol were tested. The aim of the study was to optimize the operating conditions to maximize production yields while minimizing the particle size. The characterization of microsphere revealed the poor flow ability of the spray-dried products due to significant cohesiveness and very small size (less than 20μm).

Yupeng Lu et al.[30] Hollow hydroxyapatite microspheres were prepared using a simple spray drying method. The incorporation of ammonium bicarbonate could produce carbon dioxide and ammonia gas bubbles during the spraying, and thus created a hollow inner structure in the resultant microspheres. The hollow microspheres prepared using different amounts of ammonium bicarbonate were also characterized. These microspheres were composed of nanoparticles with an average crystallite size of 15 nm. A high surface area (80 m2/g) and porosity of the microspheres could be achieved when the concentration of ammonium bicarbonate was about 5 wt%.

Fourier transform infrared results showed that CO3 2− was incorporated into the HA microspheres. These hollow microspheres have many potential uses such as injectable drug-delivery carriers.

Muzzarelli A A et al.[31] Incubation of the rigid and transparent gel obtained upon pouring a chitosan hydrochloride solution into saturated ammonium hydrogen carbonate at 20 8C yielded chitosan carbamate, soluble at alkaline pH values, typically 9.6. Addition of water to the gel isolated by centrifugation promoted the dissolution of the gel. By spray-drying the alkaline solution thus obtained, microspheres of chitosan were obtained. When chitosan carbamate was mixed with alginic acid, polygalacturonic acid, carboxymethyl cellulose, carboxymethyl guaran, acacia gum, 6-oxychitin, xanthan, hyaluronic acid, pectin, k-carrageenan, and guaran, clear solutions were obtained from which chitosan–polyuronan microspheres were easily manufactured by spray-drying. Those made of chitosan–xanthun or chitosan–guaran were

unexpectedly found to be soluble in water; similarly, the chitosan–pectin microspheres were almost soluble. The microspheres containing hyaluronic acid or k-carrageenan underwent swelling when contacted with water; the other ones were insoluble. The microspheres were characterized by FTIR, X-ray diffraction spectrometry and scanning electron microscopy. The structural alterations detected were mainly due to interactions between the amino groups and the carboxyl groups.

Dolores Blanco M et al.[32] Ketotifen (KT)-loaded chitosan microspheres (MS) were prepared for controlled release of the antihistaminic drug, and their use as delivery systems in the intraperitoneal cavity of rats was investigated. Microspheres were prepared by a spray-drying method followed by treating with glutaraldehyde solutions in methanol as cross-linker.

Results showed that very small spherical microspheres (1.0–1.3 lm) with a high load of KT (92 ± 6 lg KT/mg) were obtained. KT loading decreased with cross-linking (52 ± 2– 46 ± 7 lg KT/mg). Interactions between KT and chitosan avoided total KT release from cross-linked MS. After intraperitoneal (i.p.) administration, microsphere aggregations were adhered to muscle subjacent

to the tegument and to adipose tissue, and there were no evident sings of rejection; KT was detected in blood stream (0.37–0.25 lg/mL) at 24 h, which was longer than the i.p. administration of the drug in solution (39.4 lg/mL at 2.4 hr).

Hildgen P et al.[33] The morphology, the surface structure, and the mean diameter of spray-dried biodegradable pegylated microspheres were studied by X-ray photoelectron spectroscopy (XPS) technique, scanning electron microscopy (SEM) and photo correlation spectroscopy. PEG 400-distearate (PEG-400(C18)2) was incorporated into poly(D,L-lactic acid) (PLA) by spray-drying using different concentrations of PLA and polyethylene glycol-distearate (PEG-distearate). The use of these different concentrations resulted in systems with different sizes, morphologies and surfaces. Microsphere characteristics such as size distribution, morphology, and PEG distribution were investigated and proven to be highly dependent on the concentrations of PLA and PEG in the solutions to be spray-dried. Scanning electron microscopy showed that the PLA concentration in the polymeric solution rise to microparticles rather than microspheres. Red blood cell-like structures were observed for a high PLA concentration. Photo correlation spectroscopy proved that the size distribution depended on the initial viscosity of the polymeric solution. The more viscous was the solution, the bigger the microspheres (and vice versa). X-ray photoelectron spectroscopy confirmed the assumption that greater is the amount of PEG-distearate in the formulation, the more it is found on the surface. These results have allowed us to predict pegylated biodegradable microspheres to be the best microencapsulation process.

Pirjo Kortesuo et al.[34] The objective of this study was to evaluate sol–gel-derived spray dried silica gel microspheres as carrier material for dexmedetomidine HCl and toremifene citrate. The drug was dissolved in sol–gel processed silica sol before spray drying with Bu¨ chi laboratory scale equipment. Microspheres with a low specific surface area were spherical by shape with a smooth surface without pores on the external surface. The particle size distribution was quite narrow. The in vitro release of toremifene citrate and dexmedetomidine HCl showed a dose-dependent burst followed by a slower release phase, that was proportional to the drug concentration in the concentration range between 3.9 and 15.4 wt.%. The release period for toremifene citrate was approximately 10 days and for dexmedetomidine HCl between 7 and 50 days depending on drug concentration. Spray drying is a promising way to produce spherical silica gel particles with a narrow particle size range for controlled delivery of toremifene citrate and dexmedetomidine HCl.

Palmieri F et al.[35] Ketoprofen controlled release microspheres were prepared, by emulsion /solvent evaporation, at 15 °C, in order to avoid the formation of semisolid particles. An identical procedure was carried out at 60 °C to speed up the solvent evaporation and the formed semisolid microspheres were directly microencapsulated by complex coacervation and spray-dried in order to recover them as free flowing powder. Microspheres and microcapsules were characterized by

scanning electron microscopy, differential scanning calorimetry, X-ray diffractometry, in vitro dissolution studies, and then used for the preparation of tablets. During this step, the compressibility of the prepared powders was measured. Microspheres and microcapsules showed compaction abilities by far better than those of the corresponding physical mixtures. In fact, it was impossible to obtain tablets by direct compressing drug and polymer physical mixtures, but microspheres and microcapsules were easily transformed into tablets.

Finally, in vitro dissolution studies were performed and the release control of the tablets was pointed out. Microspheres were able to control Ketoprofen release only after their transformation into tablets. Tablets containing eudragit RS were the most effective in slowing down drug release.

Paolo Giunchedi et al.[36] The work purpose was to study the application of 5-methylpyrrolidinone chitosan (MPC) for preparing mucoadhesive microparticles for the nasal administration of drugs. Microspheres were produced by the spray-drying technique using MPC; metoclopramide hydrochloride (MC) was chosen as model drug. Chitosan microparticles were prepared as a comparison. The microparticles obtained were characterized (encapsulation efficiency, morphology, size and drug release behavior). In-vitro mucoadhesive tests, swelling tests and ex-vivo studies using sheep nasal mucosa were performed. The hydrogel formation from microspheres was studied in different media and at different pHs. Microspheres are able to control the in-vitro MC release. MPC microparticles show good in-vitro mucoadhesive properties and ex-vivo controlled permeation profiles. The hydrogel formation is dependent mainly on the medium used: ionically cross linked hydrogel was hypothesized. These in-vitro and ex-vivo preliminary results show that spray-dried microspheres based on MPC could be a suitable nasal delivery system for the administration of metoclopramide.

Rajesh R. Parikh et al.[37] The objective of this research was to optimize the processing parameters for poly(D,L-lactide-co-glycolide) (PLGA) microspheres of 5-fluorouracil (5-FU) and to mathematically relate the process parameters and properties of microspheres. Microspheres were prepared by a water-in-oil-in-water emulsion solvent evaporation technique. A 3^2 factorial design was employed to study the effect of the volume of the internal phase of the primary emulsion and the volume of the external phase of the secondary emulsion on yield, particle size, and encapsulation efficiency of microspheres. An increase in the volume of the inter-nal phase of the primary emulsion resulted in a decrease in yield and encapsulation efficiency and an increase in particle size of microspheres. When the volume of the external phase of the secondary emulsion was increased, a decrease in yield, particle size, and encapsulation efficiency was observed. Micro-spheres with good batch-to-batch reproducibility could be produced. Scanning electron microscopic study indicated that microspheres existed as aggregates.

Munday D L et al.[38] The utility of two novel linear random copolyesters to encapsulate and control the release of ibuprofen, via microspheres, was investigated. Various manufacturing parameters, including temperature, disperse phase volume and polymer ibuprofen ratios were altered during the microsphere production. The effects of these changes on the morphological characteristics of the microspheres, yield, drug loading, encapsulation efficiency and drug release rates were examined. The diameter of the microspheres ranged from 36 to 89 _m and showed both smooth and ridged surfaces. Microsphere diameter was probably determined by the internal phase volume, while surface morphology was controlled by manufacturing temperature. Greater encapsulation efficiency was obtained by increasing the polymer: ibuprofen ratio and by reducing the internal phase volume. For all batches there was an initial burst drug release into phosphate buffer (pH 7.4) over the first 2–4 hr, which was followed by a much slower release rate over the remaining time period. Drug release rates during both these phases were dependent upon the amount and nature of the polymer in the microspheres, noting that the more hydrophilic polymer provided faster release rates.

Ibuprofen solubility appeared to play a dominant role in controlling release, although both encapsulation efficiency and microsphere morphology were also contributing factors.

Patel V et al.[39] Magnetic microsphere is newer approach in pharmaceutical field. Magnetic microsphere is prepared by various techniques. It is having various applications in diagnosis and

treatment of various diseases. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200μm. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery and supplements as miniature versions of diseased organ and tissues in the body.

Dolores Blanco M et al.[40] Polymeric microsphere degradation must be taken into account in the design of drug delivery systems to be injected in *in vivo* systems, thus a prior analysis of *in vitro* degradation behavior of microspheres appears to be necessary. In this study degradation characteristics of poly (lactide*co*-glycolide) (PLGA) and poly (d, l-lactide) (PLA) microspheres prepared by the spray-drying technique have been examined. It was found that a slow decrease in molecular weight took place during the first stage of degradation, and the value of the rate constant decreased with the increase of the percentage of lactic acid of the polymer in a linear way. Thus, the period of time of this first stage decreased with the increase of content of glycolidyl units of the polymer, and it was the unique stage observed in PLA microspheres after 5 months of study.

During this period of time, significant mass loss was not observed in the microspheres. The second stage of degradation of PLGA microspheres showed a larger rate constant, whose value increased with the content of glycolidyl units of the polymer. Mass loss was observed from number-average molecular weight about 6000. A sharp decrease of glass transition temperature (*T*g) was observed coinciding with the start of mass loss. This fact was accompanied by a physical change of the samples, fusion of microspheres to form large particles, which also fusion to form a unique mass of polymer; moment from that the degradation process was quicker.

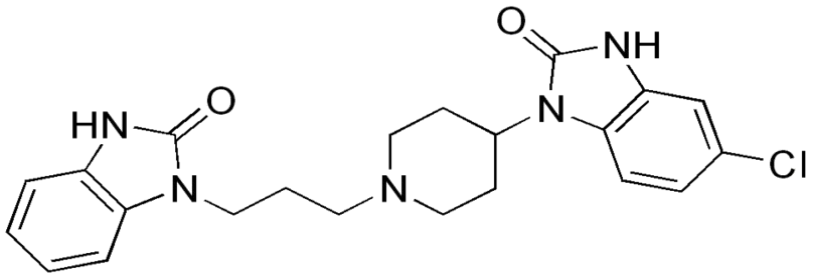
Sahu S et al.[41] The development of oral sustained or controlled release dosage form of captopril has been an interested topic of research for a long period of time. Difficulties encountered on the fact that the drug is freely water soluble. Such drug is difficult to be delivered orally in a sustained or controlled release manner and, Due to its effectiveness and intensive use as a drug of choice in the treatment of hypertension and congestive heart failure, numerous sustained and controlled release formulations of captopril have been made and reported. Captropril microsphere were prepared with a coat consisting of alginate and polymer such as HPMC, Sodium alginate, Sodium Carboxy methyl cellulose, by Ionic cross linking technique using CaCl2.

5.DRUG PROFILE

Generic name : Domperidone

Class : A specific blocker of dopamine receptors

Structure



Chemical Name : 5-Chloro-1-[1-[3-(2,3-dihydro-2-oxo-1*H* benzimidazol-1- yl) propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2- one

Molecular formula : $C_{22}H_{24}ClN_5O_2$

Molecular weight : 425.911

Description : White or almost white crystalline powder

Melting point : 240°c - 242°c

Half life : 4 - 5 hrs

Solubility : Very slightly soluble in water and alcohol, slightly soluble in methanol ,sparingly soluble in dimethylformamide.

Standards : Domperidone contains NLT 98.5 % and NMT 101.0 % of $C_8H_{15}N_7O_2S_3$ calculated on dried basis.

Heavy metal : Not more than 10 ppm

Sulphated Ash : Not more than 0.1 %,

Loss on drying : It loses not more than 0.5 % W/W.

Pharmacological profile: Domperidone is a third generation β receptor antagonist that has a unique pharmacological profile. It blocks β_1, β_2 and α_1 receptors. It also has antioxidant and ant proliferative effects. It has membrane-stabilizing activity but it lacks intrinsic sympathomimetic activity. Domperidone produces vasodilatation.

Mechanism of action: Domperidone acts as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant. The gastro-prokinetic properties of domperidone are related to its peripheral dopamine receptor blocking properties. Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which - among others - regulates nausea and vomiting..

Pharmacokinetic Parameters	
Bio availability	25– 30 %
Plasma half life	4-6hr(oral),3.5hr (parenteral)
Plasma protein binding	91%-93%
Excretion	Renal (33%), Feces (66%)

Table: 1

Interactions: Domperidone with Artemether, Ziprasidone, Tacrolimus, Thiothixene gives Additive QTc-prolongation may occur. It is also known to interact with other drugs like cabergoline, cinnarizine, lisuride, oxycodone, pergolide, piribedil.

Food Interactions: Take 15 to 30 minutes before meals to avoid food interactions

Adverse effects: The severe or irreversible adverse effects of Domperidone, which give rise to further complications include Tardive dyskinesia, Parkinsonism, Extrapyramidal dystonic reactions. Domperidone produces potentially life-threatening effects which include seizures, dysrhythmias, which are responsible for the discontinuation of Domperidone therapy. The signs and symptoms that are produced after the acute overdosage of Domperidone include Convulsions, Coma, GI disturbances, and Extra pyramidal effects.

Therapeutic use

- There is some evidence that Domperidone has antiemetic activity
- Domperidone has also been found effective in the treatment of gastro paresis, a stomach motility condition and for pediatric-gastro esophageal reflux
- It can be used in patients with Parkinson's disease.

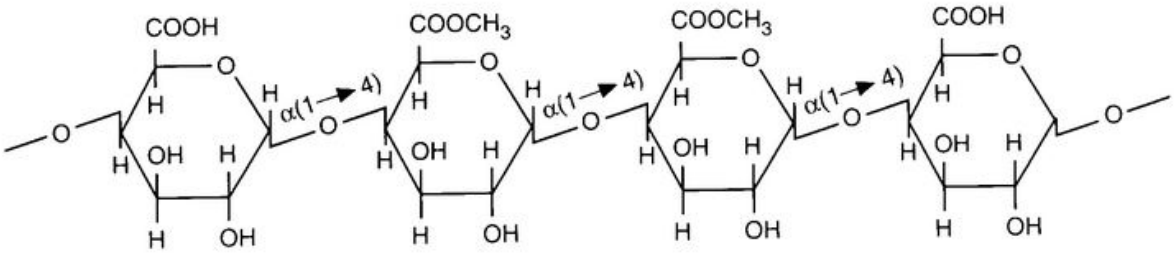
POLYMER PROFILE

PECTIN

Source : Inner portion of rind of citrus peel i.e. citrus simon or citrus aurantium (Rutaceae)

Synonyms : Citrus pectin, Poly(1,4-alpha-D-galacturonide)

Structure:



Chemical name : Poly(1,4-alpha-D-galacturonide)

Molecular weight : 60–130,000 g/mol

Description : It is an odorless and mucilaginous, Cream –yellowish powder.

Moisture content : Pectin absorbs moisture from the atmosphere, the amount of water absorbed depends upon initial moisture content and temperature and relative humidity of surrounding air.

Solubility : Pectin is soluble in pure water, partially soluble in cold water. It is insoluble in alcohol and organic solvents. When pectin is mixed with alcohol or organic solvent and mixed with water it is soluble, whereas di- and tri- salts are weakly soluble or insoluble.

Viscosity : Typical viscosity values for 1 % (w/v) aqueous solutions of Pectin viscosities measured at 10ºC. Above 70º the final viscosity is slightly reduced

TYPICAL PROPERTIES	
Acidity/alkalinity	2-8
Bulk density	580 - 600gms/lit
gel strength	90 – 110
Ash	Not more than 4%
Loss on drying	Not more than 10%

Table: 2

Functional Category: Pectin has excellent, Gelling agent, Emulsifying and thickening, rate-controlling polymer for sustained release, stabilizing agent, tablet binder and viscosity- increasing agent.

Applications:

- Pectin is used as a thickening and stabilizing agent.
- It helps to prevent oil separation by stabilizing the emulsion, although it is not an emulsifier
- Pectin is also an ingredient in some sustained-release pills.
- It is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Pectin used as adsorbent in treatment of diarrhea.
- It used as haemostatic for internal or external hemorrhage**.**
- It used as emulsifying agent, gelling agent in acidic medium and as plasma substitute.
- Used as thickening agent in sauces, jams, ketchups.
- It is more stable in acidic medium. Pectin in combination with gelatin used as encapsulating agent for sustained release.
- In the cigar industry, pectin is considered an excellent substitute for vegetable glue

Stability: Pectin is a stable material, although it is hygroscopic after drying. Pectin is stable at ordinary conditions, becomes unstable in excess heat. Pectin is combustible at higher temperatures, because of this it must be kept away from heat and any source of ignition. Viscosity, solubility and gelation are generally related (e.g. factors that increase gel strength will increase the tendency to gel, decrease solubility, and increase viscosity and vice versa At a pH of 5-6 low methylated pectin is stable, but high methoxylated pectin is stable only at room temperature

Incompatibilities: Pectin is incompatible with some oxidizing agents. Since it is nonionic, will not complex with metallic salts or ionic organics to form insoluble precipitates. Decomposition by oxides of carbon

Safety: The FAO/WHO joint Expert Committee on Food Additives and in the EU, no numerical acceptable daily intake (ADI) has been set, as pectin is considered safe. In the US, pectin is GRAS – generally recognized as safe. In most foods it can be used according to good manufacturing practices in the levels needed for its application (quantum satis).

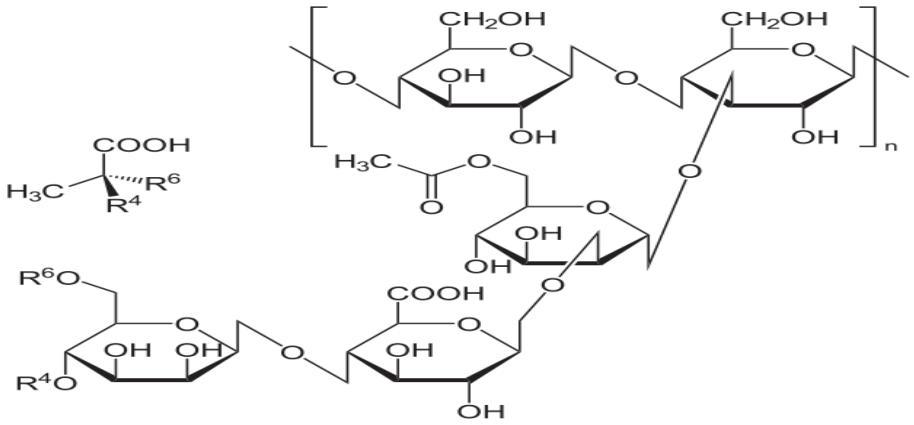
In the International Numbering System (INS), pectin has the number 440. In Europe, pectin's are differentiated into the E numbers E440 for non-amidated pectin's and E440. There are specifications in all national and international legislation defining its quality and regulating its use.

Handling precautions: Pectin dust cause mechanical irritation to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosion in air. It causes skin irritation or injury. Decomposition caused by Irritating and toxic fumes and gases. So wear safety glasses with side shields and appropriate gloves to prevent eye and skin exposure respectively

XANTHANGUM

Synonyms : Bacterial Polysaccharide, Corn Sugar Gum, Goma Xantana, Gomme de Sucre de Maïs, Polysaccharide de Type Xanthane, Polysaccharide Xanthane, Xanthan, Xanthomonas campestris.

Structure



Molecular formula : $C_{35}H_{49}O_{29}$ (monomer)

Molecular weight : 2×106 to 5×107

Description : It is an odorless and tasteless, light beige powder.

Moisture content : Xanthun gum absorbs moisture from the atmosphere. The amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Solubility : It is soluble in cold water, forming a viscous colloidal solution and practically insoluble in organic solvents

Viscosity : Typical viscosity values for 1 % (w/v) aqueous solutions of Xanthun gum viscosities measured at 10ºC. Above 80º the final viscosity is slightly reduced.

TYPICAL PROPERTIES	
Acidity/alkalinity	pH = 6-8
Density	1.5 g/cm3 (20 C)
Bulk density	550 - 700kg/m³
Moisture	13% max
Ash	13% max

Table: 3

Functional Category: Xanthangum has excellent thickening, stabilizing, pseudoplastic property and Emulsifying rate-controlling polymer for sustained release stabilizing agent, tablet binder and viscosity-increasing agent.

Applications:

- Xanthan gum is used as a thickening and stabilizing agent in foods, toothpastes, and medicines.
- It helps to prevent oil separation by stabilizing the emulsion, although it is not an emulsifier
- Xanthan gum is also an ingredient in some sustained-release pills.
- It is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations.
- Use as a bulk-forming laxative to treat constipation.
- Lowering blood sugar in people with diabetes.
- Use as a saliva substitute for dry mouth.
- In the oil industry, xanthun gum is used in large quantities, usually to thicken drilling mud.
- In cosmetics, xanthan gum is used to prepare water gels, usually in conjunction with bentonite clays.

Stability: Xanthun gum powder is a stable material, although it is hygroscopic after drying. Stability is affected by solute concentration, temperature (both the dissolving temperature and the measured solution temperature), salinity and PH value.

Xanthun gum shows high low-shear viscosity but is strongly shear-thinning. Being non-ionic, it is not affected by ionic strength or pH but will degrade at pH extremes at temperature.

Incompatibilities: Xanthun gum is incompatible with some oxidizing agents. Since it is nonionic, it will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety: The safety data on guar gum may be largely available to establish the safety. Xanthan gum is safe when up to 15 grams per day are taken. It can cause some side effects such as intestinal gas (flatulence) and bloating. The safety of Xanthun gum has been assessed by JECFA (Joint Expert Committee on Food Additives) in 1955 and by the EEC's SCF (European Economic Community, Scientific Committee on Foods) in 1964. In USA, guar gum has been considered GRAS (Generally Recognized As Safe) since 1984 in numerous food applications.

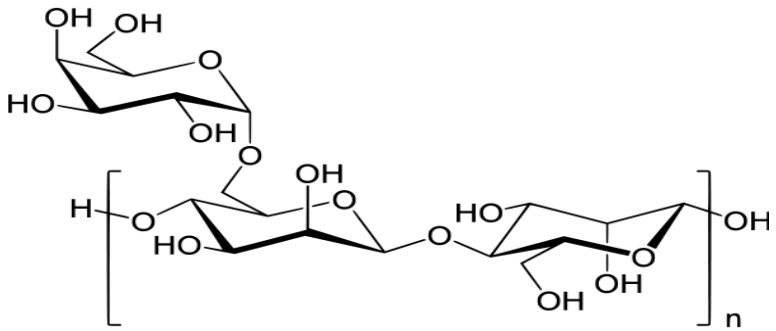
Guar gum did not elicit measurable mutagenic responses. This material is a dust or may produce dust. Breathing small amounts of this material is not likely to be harmful. Unlikely to cause skin irritation he Food and Drug Administration issued a caution that simply thick should not be fed to premature infants because it may cause necrotizing enterocolitis.

Handling precautions: Xanthun gum dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosion in air. Unlikely to cause skin irritation or injury. This material is a dust or may produce dust. Breathing small amounts of this material is not likely to be harmful.

GUARGUM

Synonyms : Guar, guar flour, jaguar gum, guaran.

Structure



Molecular weight : 2,000 to 3,000 mPa·s

Description : It is an odorless and tasteless, yellowish white coloured powder.

Moisture content : Guar gum absorbs moisture from the atmosphere the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of surrounding air.

Solubility : It is soluble in cold water, forming a viscous colloidal solution and also in hot water and practically insoluble in organic solvents.

Viscosity : Typical viscosity values for 2 % (w/v) aqueous solution of Guar gum viscosities measured at 20ºC. Above 80º the final viscosity is slightly reduced

TYPICAL PROPERTIES	
Acidity/alkalinity	pH = 3-7.0 for a 1 % w/w aqueous solution
Ash	Not more than 1%
Auto ignition temperature	360ºC
Density (bulk)	0.321 g/cm^3
Density (tapped)	0.537 g/cm^3
Density (true)	1.316 g/cm^3
Specific gravity	1.26
Melting point	Browns at 190–200 ºC. Chars at 225–230 ºC. Glass transition temperature is 170–180 ºC.

Table: 4

Functional Category: Guar gum has strong hydrogen bonding properties. It has excellent thickening, Emulsion, Stabilizing and film forming properties, rate-controlling polymer for sustained release, stabilizing agent, tablet binder and viscosity-increasing agent.

Applications

Guar gum is widely used in oral and topical pharmaceutical formulations.

- It is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations.
- As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- Solutions with different gum concentrations can be used as emulsifiers and stabilizers because they prevent oil droplets from coalescing. Guar gum is also used as suspension stabilizer

- It is 5 to 8 times ticking power than starch.
- It used as protective colloid, binding agent, bulk laxative, appetite depressant and used in peptic ulcer therapy.
- It is also used in cosmetic preparation.

Stability: Guar gum powder is a stable material, although it is hygroscopic after drying. Guar gum shows high low-shear viscosity but is strongly shear-thinning. Being non-ionic, it is not affected by ionic strength or pH but will degrade at pH extremes at temperature for e.g. pH 3 at 50°C. With case in, it becomes slightly thixotropic forming a biphasic system containing casein micelles.

Incompatibilities: Guar gum is incompatible with some oxidizing agents. Since it is nonionic, will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety: The safety data on guar gum may be largely available to establish the safety of its partially hydrolyzed analogue, PHGG. The safety of guar gum has been assessed by JECFA (Joint Expert Committee on Food Additives) in 1975 and by the EEC's SCF (European Economic Community, Scientific Committee on Foods) in 1978. In USA, guar gum has been considered GRAS (Generally Recognized As Safe) since 1974 in numerous food applications. Guar gum did not elicit measurable mutagenic responses in the host-mediated assay using Salmonella, and was not carcinogenic in either species or sex

Handling precautions: Guar gum dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risk of explosion. Guar gum is combustible.

6.MATERIALS &METHODS

METHODOLOGY

PREFORMULATION STUDY

Preformulation testing is an investigation of physical and chemical properties of drug alone and when combined with excipients. It is the first step in the rational development of dosage form.

Preformulation studies relate to pharmaceutical and analytical investigation carried out in supporting formulation development efforts of dosage form.

The following preformualtion studies were for the sample of drug.

Organoleptic Properties of Drug Powder:

Colour and nature:

Transferred small quantity of the sample on a white piece of paper to spread powder and examined visually.

Physical characteristics of drug powder:

Flow properties:

a) Bulk density (D_b): It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called intial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

Where, D_b = Bulk density (gm/cc),

M = mass of powder (g),

V_o =bulk volume of powder (cc).

b) Tapped density(D_t):

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

Where,

Dt = Tapped density(gm/cc),

M = mass of powder (g),

V_t = tapped volume of powder (cc).

c) Angle of repose(θ):

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\theta = \tan^{1}(h/r)$$ where, θ =

angle of repose

h = height of pile

r = radius of the base of the pile.

Compressability index	Flow characteristics	Hausner ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Table 05: Scale of Flowability

d) Percentage Compressibility (or) Carr's index (%):

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

S.No	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	More than40	Very very poor

Table 06: % Compressibility limits with respect to flowability

e) Hausner's Ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner ratio = Tapped density/Bulk density

Table 07: Hausner ratio limits.

Hausner's ratio	Type of flow
< 1.25	Good flow
> 1.25	Poor flow

EXPERIMENTAL

LIST OF CHEMICALS:

S.No	Chemicals used	Suppliers
1	Domperidone	Yarrow chemical products, Mumbai
2	Xanthun gum	Sd Fine Chem limited, Mumbai.
3	Pectin	Nice chemicals pvt ltd, Mumbai.
4	Calcium Chloride	Finar chemicals limited, Mumbai.
5	Guar gum	Sd Fine Chem limited, Mumbai.

Table: 8

LIST OF EQUIPMENTS:

S.No	Equipments used	Suppliers
1	Magnetic Stirrer	Model: MS: 5OO, Remi Electronics Limited.
2	UV-Spectrophotometer	Model: UV – VIS double beam spectrophotometer, Labomed inc
3	Dissolution Apparatus	Model No: 2202,Systronics
4	Hot air Oven	Model No: 912, Electronics
5	Scanning Electron Microscopy	NOVEX

Table: 9

ANALYTICAL METHODOLOGY

Development of UV spectroscopic method

Determination of absorption maxima: Absorption maxima or the wavelength at which absorption takes place for accurate analytical work is important to determine the absorption maxima of the substance under study.

Method: UV method

Equipments: UV-VIS spectrophotometer

100mg of domperidone was dissolved in 100ml methanol. 1ml of this solution was pipette out in separate volumetric flask and diluted with phosphate buffer 7.4 and subjected for UV scanning in the range of 200-800 using Double beam UV-VIS spectrophotometer, (pharmaspec-1700, shimadzu, japan). The absorption maxima obtained at 284nm with a characteristic peak.

Preparation of calibration curve: Using this absorption maxima a standard curve was prepared in the concentration range of 2-10 µg/ml.

Method: UV method

Equipments: Double beam UV-VIS spectrophotometer.

Reagents: Methanol, phosphate buffer pH 7.4, domperidone.

For the preparation of calibration curve stock solution was prepared by dissolving 100mg of accurately weighed domperidone in 100ml of methanol. Further 1ml of this solution was pipette into 1 00ml of volumetric flask and diluted to 100ml with phosphate buffer7.4 solution.

From this pipette out 2,4,6,8 and 10ml into a series of 10ml volumetric flask and was made up to 10ml with phosphate buffer pH7.4 to get 2,4,6,8 and 10µg/ml of domperidone respectively . The optical density values of resulting solutions were measured at 284nm and recorded in the table with statistical data in table 7. Concentration versus optical density values are plotted and given in the figure1.

S.No.	Time in hours	Absorbance
1	0	0
2	2	0.033
3	4	0.064
4	6	0.092
5	8	0.123
6	10	0.154

Table 10: Calibration curve data for domperidone

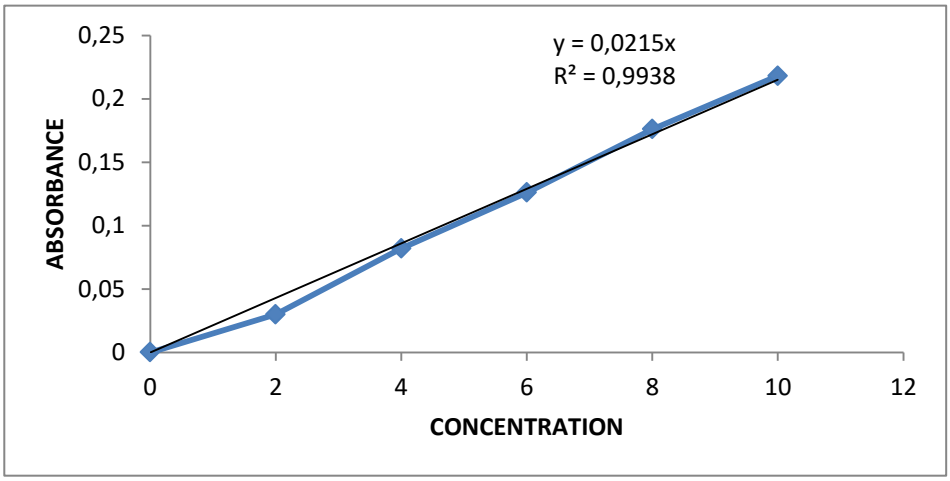


Fig: 1 STANDARD GRAPH OF DOMPERIDONE

Preformulation studies

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable, efficacious and safe dosage form.

Hence preformulation studies were carried out on the obtained samples of drug for identification and compatibility studies.

- **Identification of Drug:**

  The obtained sample was examined by infrared absorption spectral analysis and was compared with the reference standard IR spectrum of domperidone.

Method: IR Spectra of drug and drug-excipients blends were recorded on an IR spectrophotometer (Shimadzu Corporation, Japan) in the range of 4000-400 Cm^{-1} using potassium bromide discs

- **Determination of Melting point**

  Melting point of domperidone was determined by open capillary method. Melting-point apparatus is most often used for the determination of the melting point of a solid. A few crystals of the compound are placed in a thin walled capillary tube 10-15 cm long, about 1 mm in inside diameter and closed at one end.

- **Determination of solubility**

  The known excess amount of drug was added to 5 ml of water, phosphate buffer pH6.8, methanol and DMSO and these samples were rotated at 20 rpm in a water bath (37 ± 0.5°C) for 2hours. The samples were then filtered through 0.45 µm membrane filter, suitably diluted, and analyzed visually.

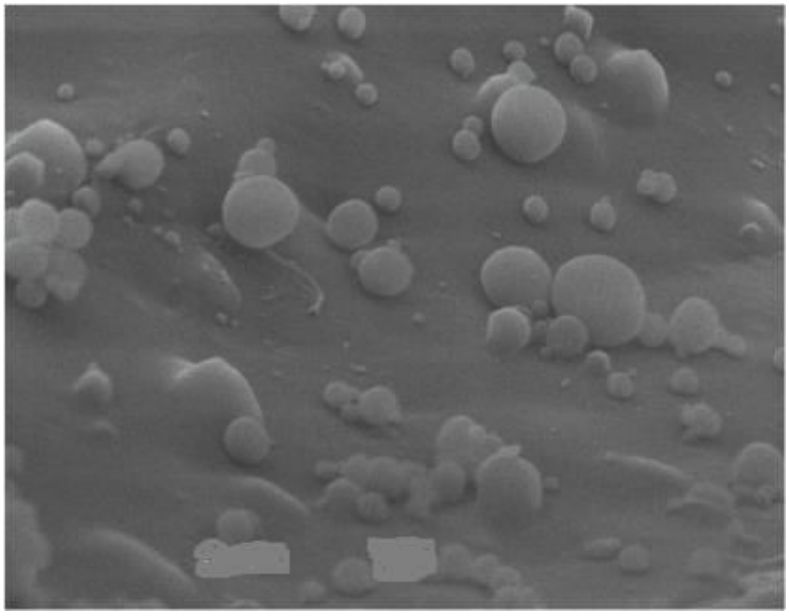
- **Compatibility Studies**

The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy. Study of drug–excipients compatibility is an important process in the development of a stable solid dosage form. Drug–excipients compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form.

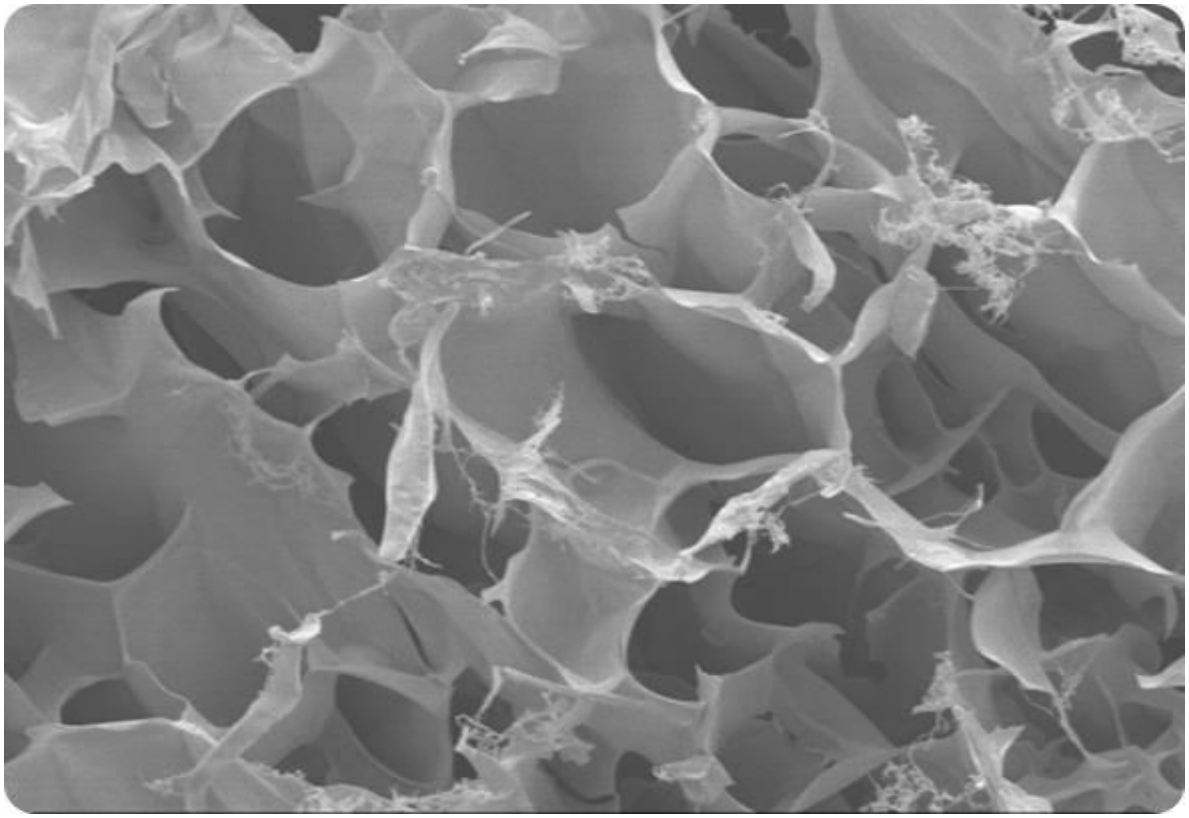
- **Scanning electron microscopy (SEM):**

Scanning Electron Microscopy - SEM - is a powerful technique in the examination of materials. It is used widely in metallurgy,geology, biology and medicine. SEM is operated under high vacuum the specimens that can be studied must be compatible with high vacuum (~ 10-5 mbar). This means that liquids and materials containing water and other volatile components cannot be studied directly. Also fine powder samples need to be fixed firmly to a specimen holder substrate so that they will not contaminate the SEM specimen chamber. Non-conductive materials need to be attached to a conductive specimen holder and coated with a thin conductive film by sputtering or evaporation. Typical coating materials are Au, Pt, Pd, their alloys, as well as carbon. There are special types of SEM instruments such as variable-pressure SEM (VPSEM) and environmental

SEM (ESEM) that can operate at higher specimen chamber pressures thus allowing for non-conductive materials (VP-SEM) or even wet specimensto be studied (ESEM). All SEM images are in black-and-white, although they may subsequently have false colours applied to them for aesthetic reasons or to aid interpretation.



Picture of Scanning Electron Microscopy.



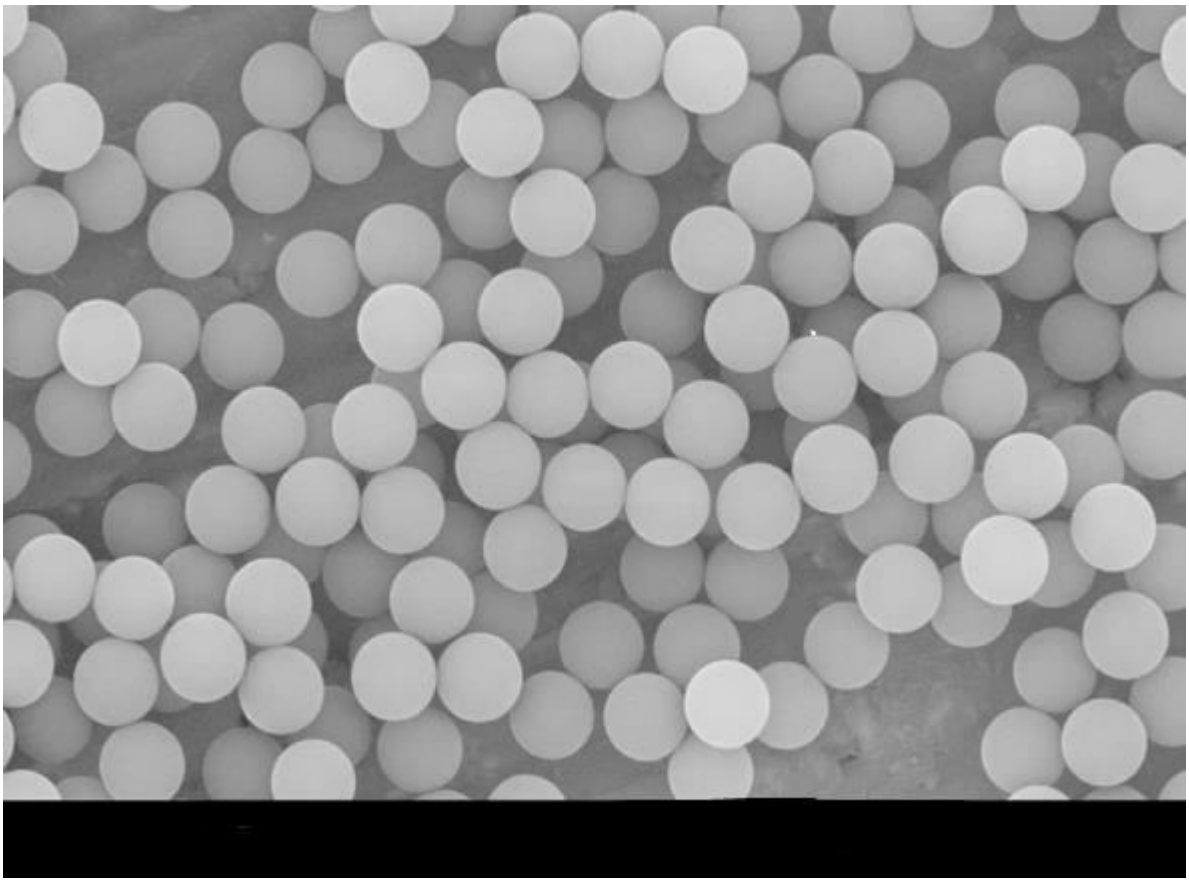
SEM analysis was performed to identify themorphology. The samples were coated with gold using Hummer sputter coater (Techniques, Ltd.), then carried using a Jeol JSM-840 scanning electron microscope (Jeol USA, Inc.,Peabody, MA), and captured the images using a digital capture cardand Digital Scan Generator 1 (Jeol). SEM can provide information on surface topography, crystalline structure, chemical composition and electrical behaviour of the top 1 urn or so of specimen. Scanning electron microscopy can provide a variety of imaging techniques with resolutions in the range 1 pm to 1 nm, depending on the microscope and the signal used to form the image.

PREPARATION OF MICROPARTICLES

Microparticles of Domperidone were prepared by ionic gelation technique. Accurately weighed quantity of drug was dissolved in sufficient quantity of distilled water. In another beaker, suitable amount of pectin was taken and mixed well with 20 ml of water. The drug solution was added to the polymer solution with stirring to produce viscous form.

The drug solution is to be mixed with all the three polymers that are used in the formulations according to the ratios mentioned in the protocol.

Then polymer drug solution was added drop wise by using syringe of 22 G in diameter from a height of about 5cms into a beaker containing 4% w/v solution of calcium chloride with continuous stirring by magnetic stirrer. Then the solution was filtered by using whatmann filter paper no-1. The microparticles were washed with water and stored in well-closed container for further use.



Picture of Microparticles

LIST OF MICROPARTICLES OF DOMPERIDONE

S.NO	FORMULATION CODE	DRUG:POLYMER RATIO(domperidone: pectin:guar gum: xanthun gum)	BATCH SIZE(mg) DRUG+POLYMER
1.	F1	1:1:0:0	50+100
2.	F2	1:2:2:0	50+200+200
3.	F3	1:2:4:0	50+200+400
4.	F4	1:4:2:0	50+400+200
5.	F5	1:4:2:4	50+0+0200+200
6.	F6	1:0:4:2	50+0+400+200
7.	F7	1:2:2:4	50+0+200+400
8.	F8	1:2:0:2	50+200+0+200
9.	F9	1:1:0:2	50+100+0+200
10.	F10	1:2:0:1	50+200+0+100

Table: 11

EVALUATION OF MICROPARTICLES

Swelling studies:

A known weight (50 mg) of microparticles were placed in little excess of distilled water, 0.1N Hcl and PBS (pH 7.4) and allowed to swell to constant weight. The microparticles were removed, blotted with filter paper and their changes in weight were measured at certain intervals and recorded. The degree of swelling (a) was then calculated from the formula:

$$a = Wg\text{-}Wo / Wo$$

where, Wo = initial weight of the beads

Wg = Weight of beads/microparticles at equilibrium swelling in medium.

Entrapment efficiency:

Drug entrapment efficiency of Domperidone microparticles was performed by accurately weighing 50 mg of microparticles and suspended in 100ml of PBS of pH7.4 and it was kept aside for 24 hours. Then, it was stirred for 15 mins and filtered. After suitable dilution, Domperidone content in the filtrate was analyzed spectrophotometrically at 284 nm using U.V. spectrophotometer.

$$\text{Entrapment Efficiency} = \frac{\text{Estimated drug content}}{\text{Theoritical drug content}} \times 100$$

Percentage yield:

The total amount of microparticles obtained was weighed and the percentage yield calculated by taking into consideration the weight of the drug and polymer.

$$\text{Yield (\%)} = \frac{\textbf{Weight of microsphere}}{\textbf{Total expected weight of drug and polymer}} \times 100$$

Particle size analysis:

Different sized microparticles were determined by using calibrated eye piece micrometer and stage micrometer. The average size of the particles is determined by

$$D\ avg = End/\ En$$

Drug content:

Microparticles equivalent to 50mg were accurately weighed and transferred to 50ml volumetric flask. Solvent was added to dissolve the microparticles and made up to the mark with same solvent. From this, further suitable dilutions were made and the drug content analyzed by UV spectrophotometrically at 284 nm.

In vitro Dissolution Studies:

The release of Domperidone from microparticles was investigated in pH 1.2 buffer and Phosphate buffer of pH 7.4 as a dissolution medium (900 ml.) using the rotating basket method specified in USPXXIV (model TDT6P Electro lab). Sample of 100 mg microparticles were taken in the basket.

A speed of 75 rpm and temperature 37± 0.5°C was maintained throughout the experiment. At fixed intervals aliquots (5 ml) was withdrawn and replaced with fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using the U.V. spectrophotometer at 475 nm against balance.

KINETICS OF DRUG RELEASE:

To study the study kinetics, data obtained from *in vitro* release were plotted in various kinetic models.

Zero order equation:

The graph was plotted as % drug released Vs time in hours.

$$C=K_0t$$

Where, K_0 = Zero order constant in concentration/time

t =Time in hours

The graph would yield a straight line with a slope equal to K_0 and intercept the origin of the axis. The results were tabulated and graph was shown.

First order equation:

The graph was plotted as log % cumulative drug remaining Vs Time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where, C_0 = initial concentration of drug.

K= First order constant.

t=Time.

Higuchi kinetics:

The graph was plotted as % Cumulative drug released Vs square root of time.

$$Q = Kt^{1/2}$$

Where, K = constant reflecting design variable system.

t =time in hours

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release. The results were tabulated.

Korsemeyer – Peppas equation: To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs time

$$M_t / M\alpha = Kt^n$$

$$\text{Log } M_t / M\,\alpha = \log K + n \log t$$

Where, $M_t / M\alpha$ =fraction of drug released at time t

t =Release time

K = Kinetic constant (incorporating structural and geometric characteristics of preparation)

n = Diffusional exponent indicative of the mechanism drug release.

If n value is 0.5 or less, the release mechanism follows " Fickian diffusion" and higher values of $0.5 < n < 1$ for mass transfer follow a non- fickian model (anamalous transport). The drug release follows zero-order drug release and case – II transport if the value is 1. For the values of n higher than 1, the mechanism of drug release is regard as super case II transport. This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time. The results were tabulated.

- Zero Order Reaction - % Cumulative drug release Vs Time in hours
- Korsmeyer – Peppas equation - log cumulative % of drug released Vs log time
- Higuchi kinetics - % Cumulative drug release Vs square root of time
- First Order Reaction – Log % Cumulative drug remaining Vs Time in hours

7.RESULTS &DISCUSSIONS

A successful attempt was made to formulate domperidone microparticles using different polymers. Effect of polymers applied on formulations was assessed. In the present work ten formulations were prepared whose composition is mentioned in Table 8. The formulated microparticles were characterized for various physicochemical parameters.

PREFORMULATION STUDIES OF PURE DRUG:

Identification of Domperidone:

The IR spectrum of pure drug was found to be similar to that of standard spectrum of Domperidone. The spectrum of Domperidone shows the following functional groups N ─ H, C ─ H, C ═ O, C ─ N at their frequencies shown in 3360 cm^{-1}, 3104 cm^{-1}, 1708 cm^{-1}, 1675 cm^{-1}.

Determination of melting point

The melting point of Domperidone was found to be 241ºC which complied with the BP standards.

Determination of solubility

Solubility of Domperidone in various solvents reveals that it was slightly soluble in alcohol, freely soluble in dimethyl sulfoxide and soluble in methylene chloride, methanol. Practically insoluble in water and in dilute acids. Sparingly soluble in ethyl ether.

Drug - polymer Compatibility Studies:

Compatibility studies of pure drug Domperidone with polymers were carried out prior to the formulation of microparticles. IR spectra of pure drug and polymers were taken, which are depicted in Figures 2, 3, 4. All the characteristic peaks of Domperidone were present in spectra at respective wavelengths. Thus, indicating compatibility between drug and polymers. It shows that there was no significant change in the chemical integrity of the drug.

DOMPERIDONE	PELLET	26/06/2013	4:25:55PM

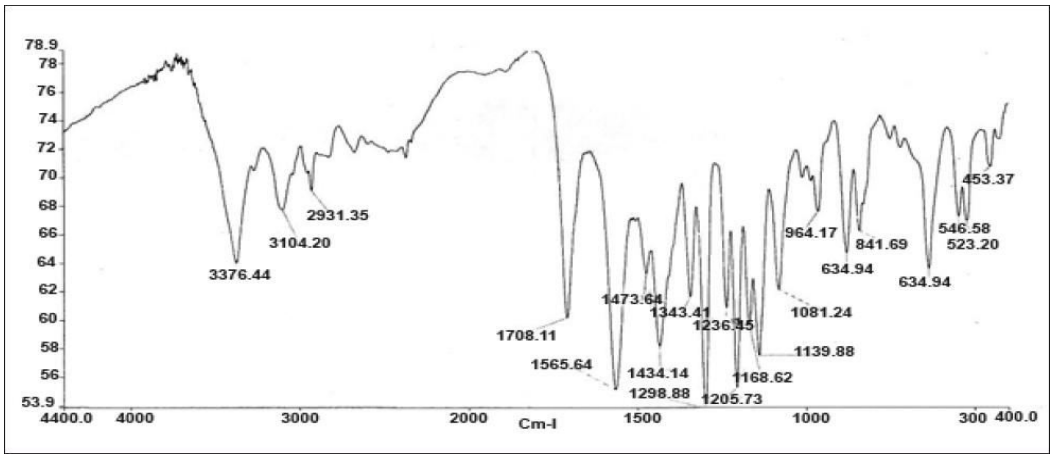


Figure 2: FTIR Spectrum of Pure Drug

PECTIN	PELLET	26/06/2013	4:25:55PM

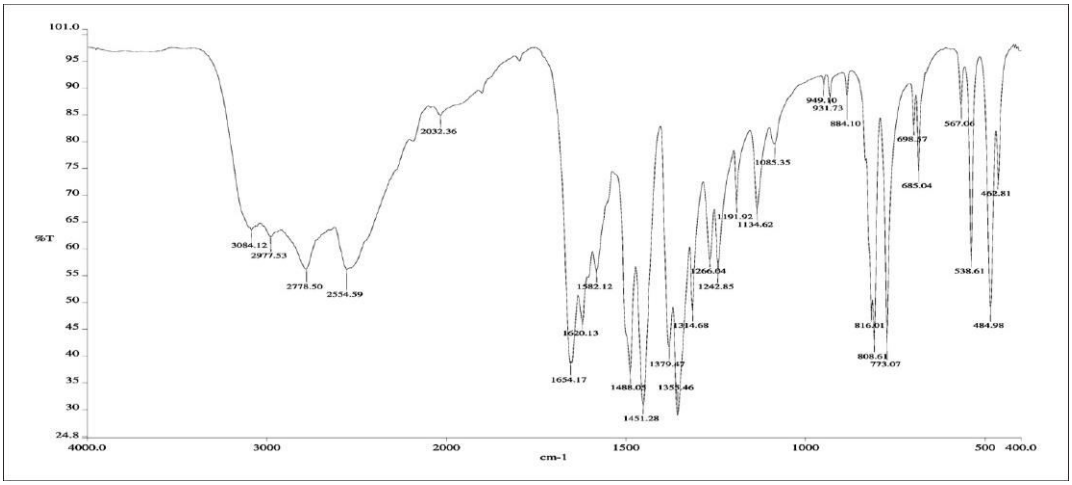


Figure 3: FITR Spectrum of Polymer Pectin

XANTHAN GUM	PELLET	26/06/2013	4:25:55PM

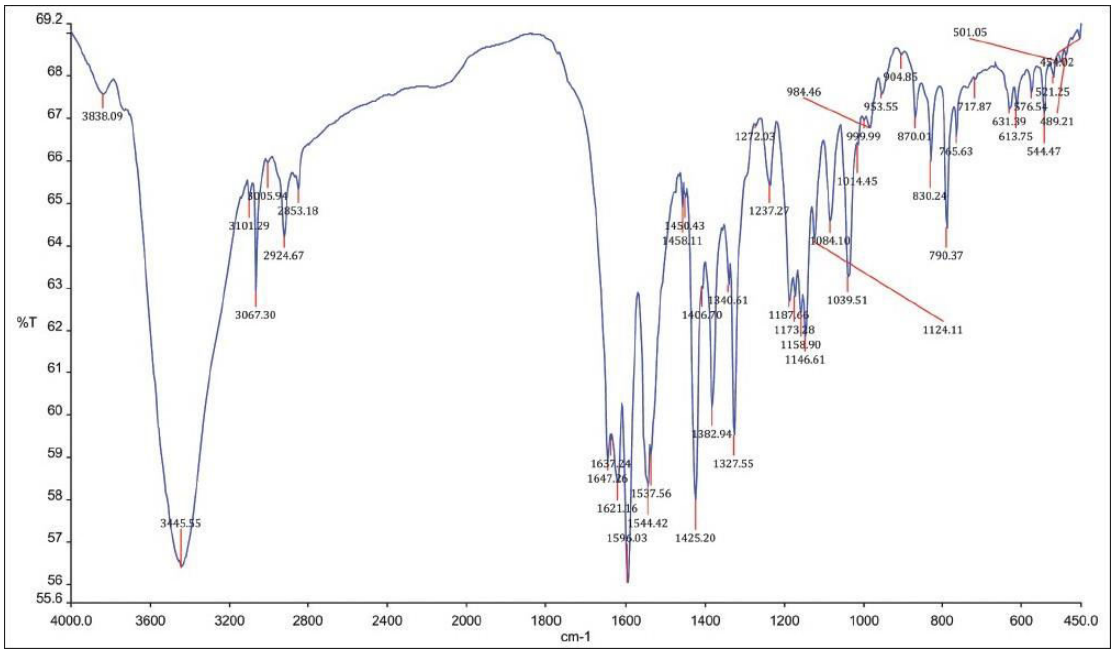


Figure 4: FTIR Spectrum of polymer Xanthun Gum

FTIR Spectrum of Drug and Polymers for the Functional Groups assigned

Polymer	Groups assigned			
	C ═ O stretch	N ─ H stretch	C ─ H stretch	C ─ N stretch
Domperidone	1708 cm^{-1}	3360cm^{-1}	3104.20cm^{-1}	1675cm^{-1}
Pectin	1620.13cm^{-1}	3084.12cm^{-1}	2977.53cm^{-1}	1654.17Cm^{-1}
Xanthun gum	1637.24cm^{-1}	3445.55cm^{-1}	3067.30cm^{-1}	1647.26cm^{-1}

Table: 12

PHYSIOCHEMICAL EVALUATION OF DOMPERIDONE MICROPARTICLES

Table: 10

Formulation code	Morphology	Percentage yield(%)	Entrapment efficiency (%)	Particle size (µm)
F1	Spherical & smooth	40.0	23.1	23.68
F2	Spherical & smooth	46.0	36.2	23.76
F3	Spherical & smooth	60.1	53.0	23.71
F4	Spherical & smooth	80.0	72.8	24.02
F5	Spherical & smooth	88.83	80.24	24.14
F6	Spherical & smooth	85.0	73.12	24.30
F7	Spherical & smooth	88.5	78.3	25.39
F8	Spherical & smooth	83.23	76.22	23.26
F9	Spherical & smooth	81.22	74.62	22.23
F10	Spherical & smooth.	80.42	72.29	21.39

Table : 13

Entrapment Efficiency Parameters:

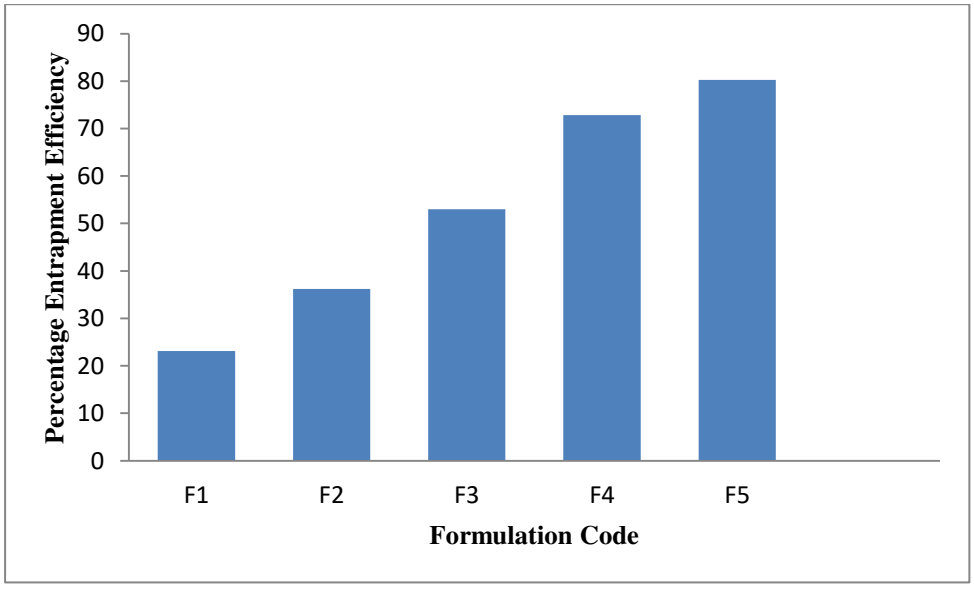


Figure 5: Entrapment Efficiency for F1 to F5 Formulations

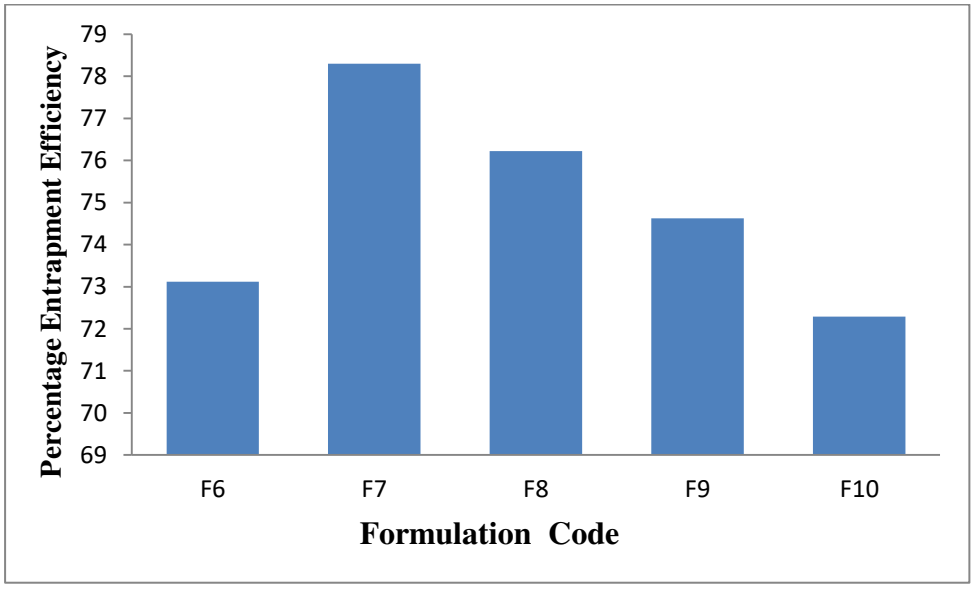


Figure 6: Entrapment Efficiency for F1 to F5 Formulations

In vitro Dissolution Studies:

In vitro dissolution studies of all the formulations of Microparticles of Domperidone were carried out in pH 6.8 phosphate buffer. The study was performed for 24 hrs, and cumulative percentage drug release was calculated at different time intervals. The *invitro* drug release profiles for the formulations were tabulated in tables 11 to table 20. The plot of time Vs. Cumulative % drug release for formulations F1 to F10 were plotted and depicted in Figures 7 and 16. Effects of various polymers and their concentration on drug release were studied

Invitro Dissolution Studies Of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.030	0.33	0.03	6.666667	0.00	0.00	6.67	11.17
2	1	0.039	0.43	0.04	8.666667	0.03	0.05	8.72	14.61
3	2	0.046	0.51	0.05	10.22222	0.04	0.09	10.32	17.28
4	4	0.074	0.82	0.08	16.44444	0.05	0.14	16.59	27.80
5	8	0.091	1.01	0.10	20.22222	0.08	0.23	20.45	34.26
6	12	0.117	1.42	0.14	28.4	0.10	0.33	28.73	48.14
7	18	0.133	1.48	0.15	29.55556	0.14	0.47	30.03	50.31
8	24	0.149	1.66	0.17	33.11111	0.15	0.62	33.73	56.52

Table 14

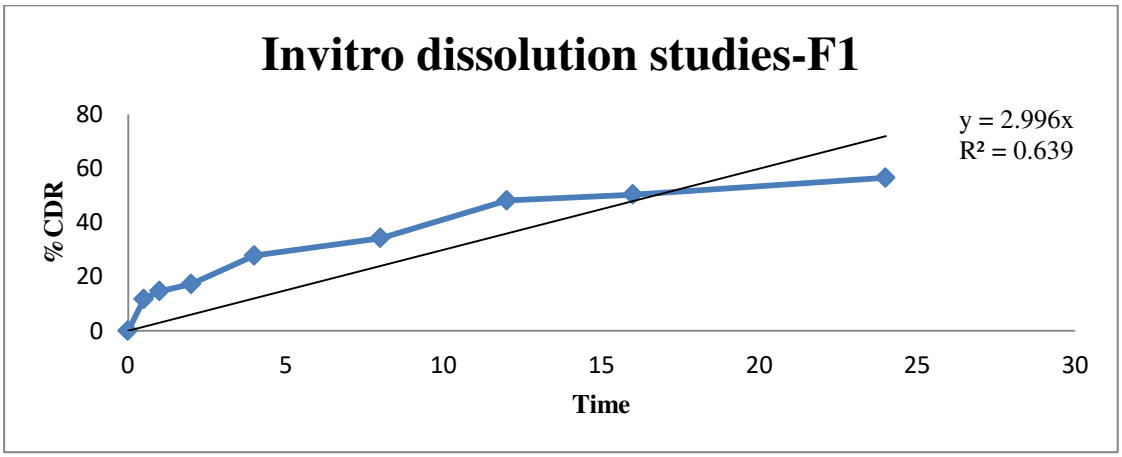


Figure: 7

Invitro Dissolution Studies of Domperidone Microparticles:

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.033	0.37	0.04	7.333333	0.00	0.00	7.33	12.29
2	1	0.052	0.58	0.06	11.55556	0.04	0.05	11.61	19.45
3	2	0.078	0.87	0.09	17.33333	0.06	0.11	17.44	29.22
4	4	0.089	0.99	0.10	19.77778	0.09	0.19	19.97	33.47
5	8	0.110	1.22	0.12	24.44444	0.10	0.29	24.74	41.45
6	12	0.129	1.42	0.14	28.4	0.12	0.42	28.82	48.28
7	18	0.145	1.61	0.16	32.22222	0.14	0.56	32.78	54.93
8	24	0.152	1.69	0.17	33.77778	0.16	0.72	34.50	57.80

Table 15

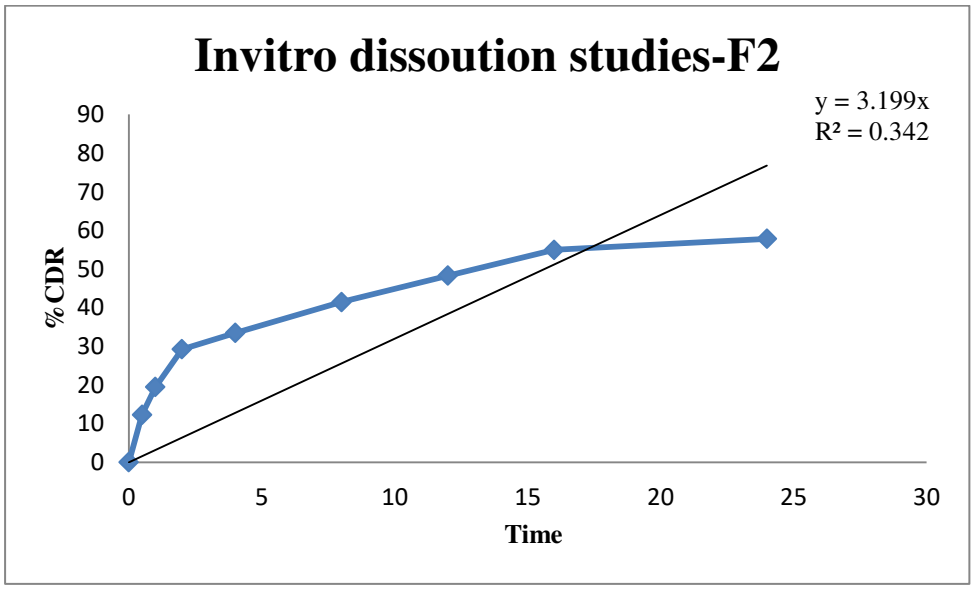


Figure: 8

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.045	0.50	0.05	10	0.00	0.00	10.00	16.76
2	1	0.059	0.66	0.07	13.11111	0.05	0.05	13.16	22.05
3	2	0.087	0.97	0.10	19.33333	0.07	0.12	19.45	32.59
4	4	0.099	1.10	0.11	22	0.10	0.21	22.21	37.22
5	8	0.119	1.32	0.13	26.44444	0.11	0.32	26.77	44.85
6	12	0.131	1.42	0.14	28.4	0.13	0.45	28.85	48.35
7	18	0.148	1.64	0.16	32.88889	0.14	0.60	33.49	56.11
8	24	0.161	1.79	0.18	35.77778	0.16	0.76	36.54	61.22

Table 16

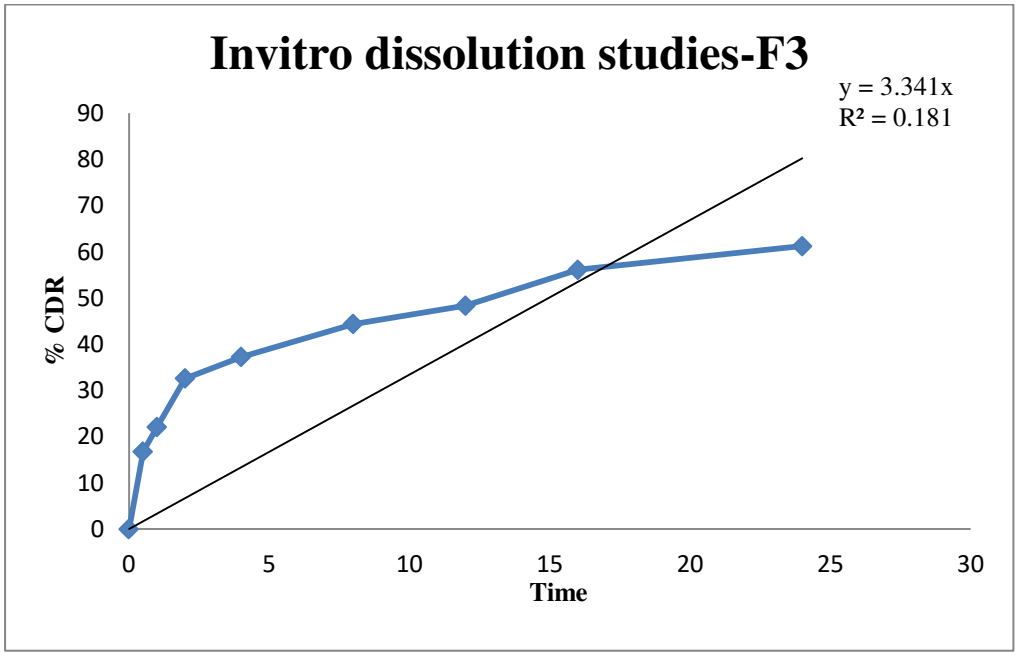


Figure: 9

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.033	0.37	0.04	7.333333	0.00	0.00	7.33	12.29
2	1	0.059	0.66	0.07	13.11111	0.04	0.05	13.16	22.05
3	2	0.067	0.74	0.07	14.88889	0.07	0.12	15.00	25.14
4	4	0.091	1.01	0.10	20.22222	0.07	0.19	20.41	34.20
5	8	0.112	1.24	0.12	24.88889	0.10	0.29	25.18	42.19
6	12	0.133	1.42	0.14	28.4	0.12	0.42	28.82	48.28
7	18	0.151	1.68	0.17	33.55556	0.14	0.56	34.11	57.16
8	24	0.172	1.91	0.19	38.22222	0.17	0.73	38.95	65.26

Table 17

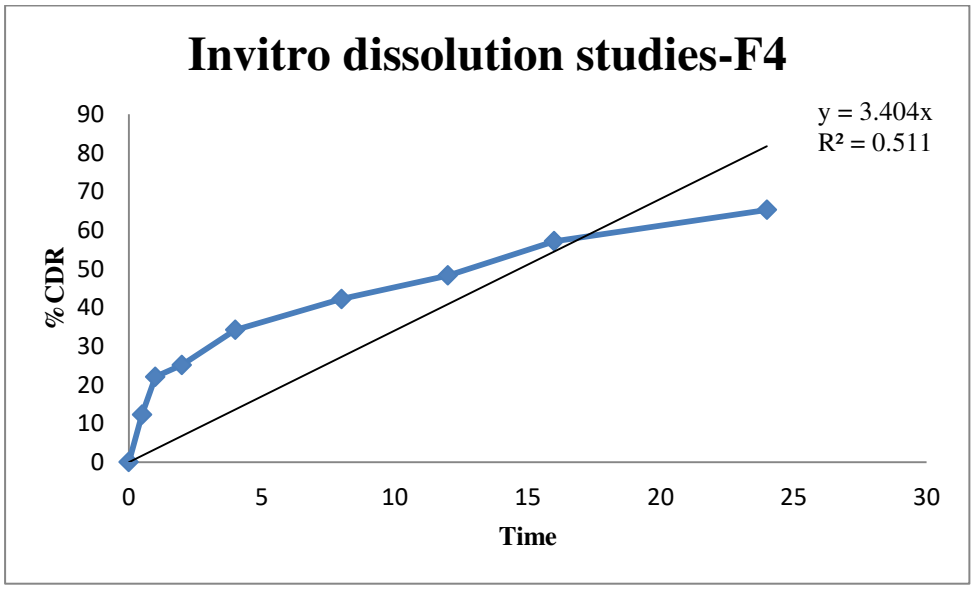


Figure: 10

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.028	0.31	0.03	6.222222	0.00	0.00	6.22	10.43
2	1	0.039	0.43	0.04	8.666667	0.03	0.05	8.72	14.61
3	2	0.067	0.74	0.07	14.88889	0.04	0.09	14.98	25.10
4	4	0.102	1.13	0.11	22.66667	0.07	0.17	22.83	38.26
5	8	0.119	1.32	0.13	26.44444	0.11	0.28	26.73	44.78
6	12	0.146	1.42	0.14	28.4	0.13	0.41	28.81	52.86
7	18	0.169	1.88	0.19	37.55556	0.14	0.56	38.11	63.86
8	24	0.186	2.07	0.21	41.33333	0.19	0.74	42.08	70.50

Table 18

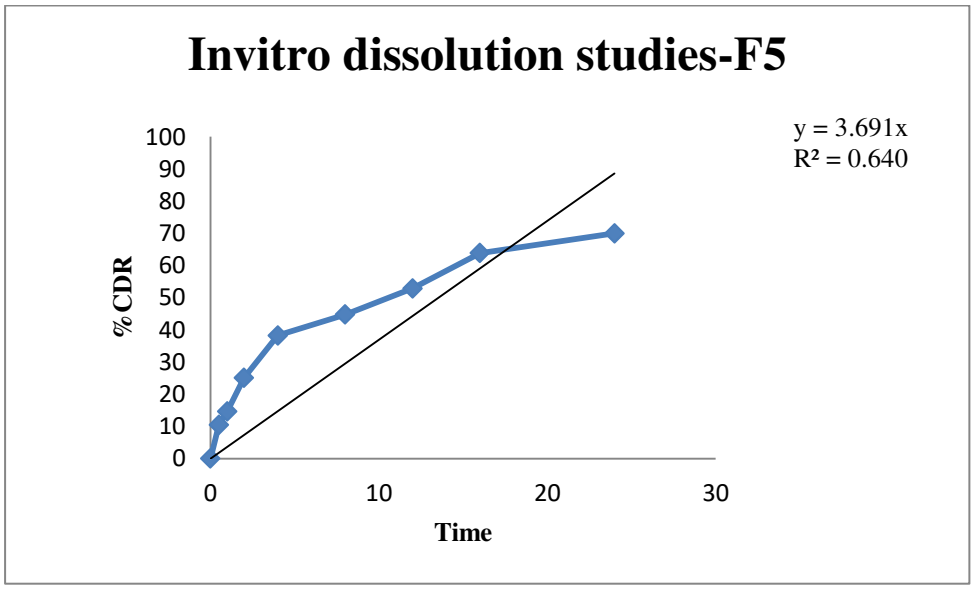


Figure: 11

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.039	0.43	0.04	8.666667	0.00	0.00	8.67	14.52
2	1	0.052	0.58	0.06	11.55556	0.04	0.05	11.61	19.45
3	2	0.085	0.94	0.09	18.88889	0.06	0.11	19.00	31.83
4	4	0.111	1.23	0.12	24.66667	0.09	0.20	24.87	41.67
5	8	0.139	1.54	0.15	30.88889	0.12	0.33	31.21	52.30
6	12	0.159	1.42	0.14	28.4	0.15	0.48	28.88	59.57
7	18	0.176	1.96	0.20	39.11111	0.14	0.62	39.73	66.58
8	24	0.193	2.14	0.21	42.88889	0.20	0.82	43.71	73.23

Table 19

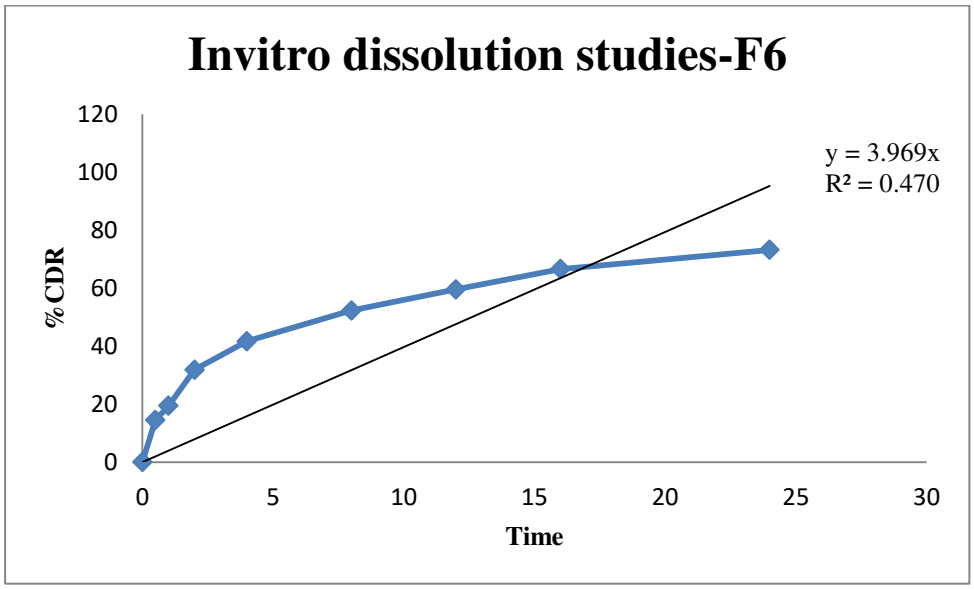


Figure: 12

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.036	0.40	0.04	8	0.00	0.00	8.00	13.40
2	1	0.051	0.57	0.06	11.33333	0.04	0.05	11.38	19.07
3	2	0.085	0.94	0.09	18.88889	0.06	0.11	19.00	31.83
4	4	0.120	1.33	0.13	26.66667	0.09	0.20	26.87	45.02
5	8	0.155	1.72	0.17	34.44444	0.13	0.33	34.78	58.28
6	12	0.163	1.42	0.14	28.4	0.17	0.51	28.91	62.39
7	18	0.176	1.96	0.20	39.11111	0.14	0.65	39.76	66.62
8	24	0.201	2.23	0.22	44.66667	0.20	0.84	45.51	76.26

Table 20

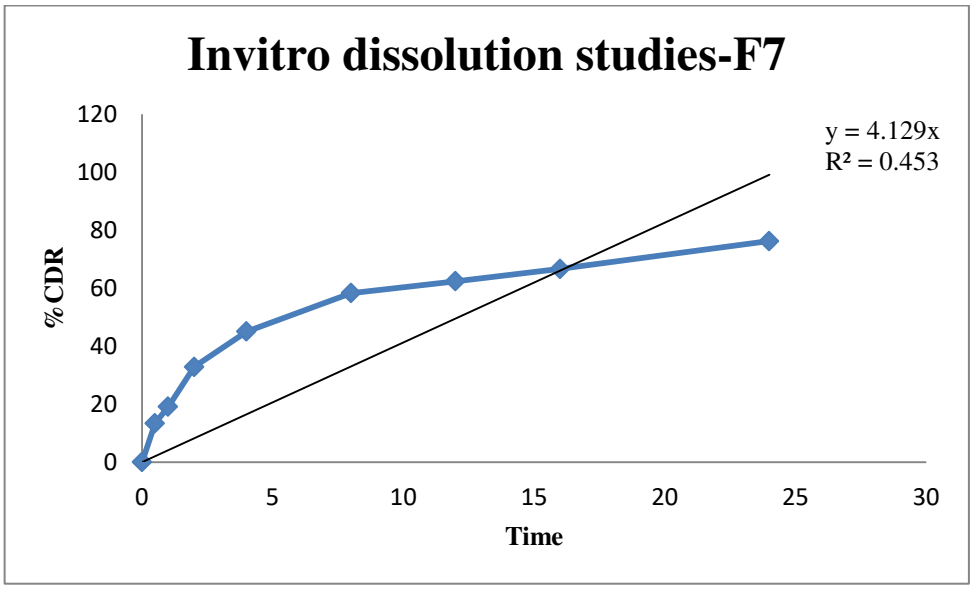


Figure: 13

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.031	0.34	0.03	6.888889	0.00	0.00	6.89	11.54
2	1	0.051	0.57	0.06	11.33333	0.03	0.05	11.38	19.07
3	2	0.078	0.87	0.09	17.33333	0.06	0.11	17.44	29.22
4	4	0.098	1.09	0.11	21.77778	0.09	0.19	21.97	36.81
5	8	0.120	1.33	0.13	26.66667	0.11	0.30	26.97	45.19
6	12	0.147	1.42	0.14	28.4	0.13	0.44	28.84	52.89
7	18	0.175	1.94	0.19	38.88889	0.14	0.58	39.47	66.13
8	24	0.189	2.10	0.21	42	0.19	0.77	42.77	71.67

Table 21

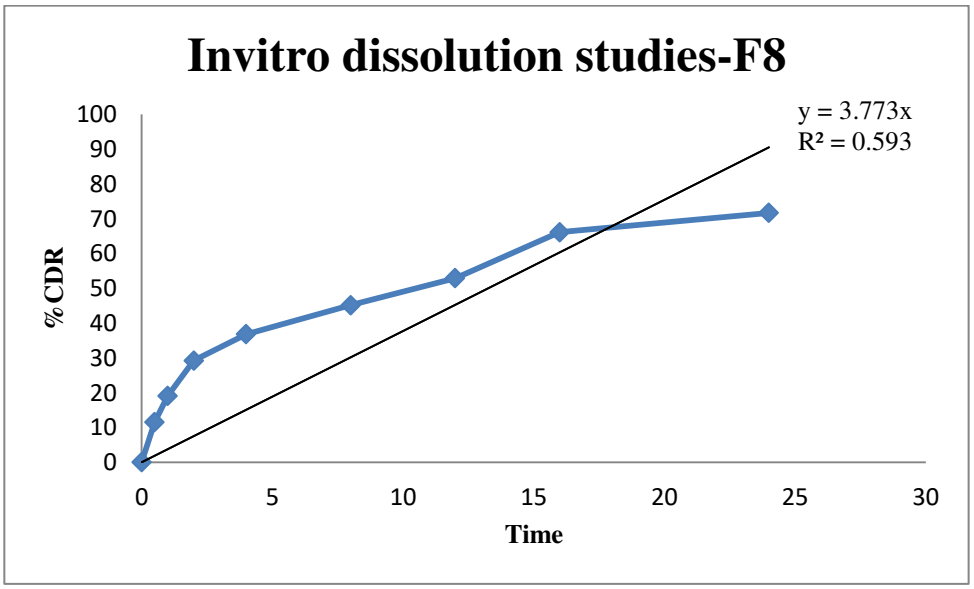


Figure: 14

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.039	0.43	0.04	8.666667	0.00	0.00	8.67	14.52
2	1	0.051	0.57	0.06	11.33333	0.04	0.05	11.38	19.07
3	2	0.072	0.80	0.08	16	0.06	0.11	16.11	26.99
4	4	0.089	0.99	0.10	19.77778	0.08	0.19	19.96	33.45
5	8	0.111	1.23	0.12	24.66667	0.10	0.29	24.95	41.81
6	12	0.131	1.42	0.14	28.4	0.12	0.41	28.81	49.63
7	18	0.149	1.66	0.17	33.11111	0.14	0.55	33.66	56.40
8	24	0.177	1.97	0.20	39.33333	0.17	0.72	40.05	67.11

Table 22

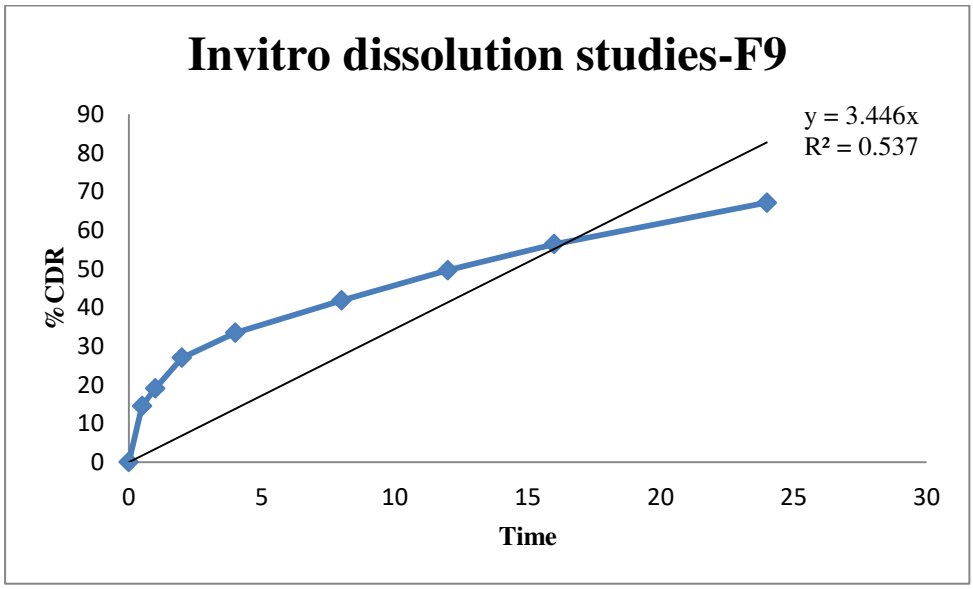


Figure: 15

Invitro Dissolution Studies of Domperidone Microparticles

S.No.	Time (h)	Abs (nm)	Con. µg/ml	Conc. Mg/ml	Conc.200 ml	Loss	CLS	CDR	% CDR
1	1	0.031	0.34	0.03	6.888889	0.00	0.00	6.89	11.54
2	1	0.058	0.64	0.06	12.88889	0.03	0.05	12.94	21.68
3	2	0.076	0.84	0.08	16.88889	0.06	0.11	17.00	28.49
4	4	0.091	1.01	0.10	20.22222	0.08	0.20	20.42	34.22
5	8	0.118	1.31	0.13	26.22222	0.10	0.30	26.52	44.44
6	12	0.129	1.42	0.14	28.4	0.13	0.43	28.83	49.63
7	18	0.158	1.76	0.18	35.11111	0.14	0.57	35.68	59.79
8	24	0.169	1.88	0.19	37.55556	0.18	0.75	38.30	64.18

Table 23

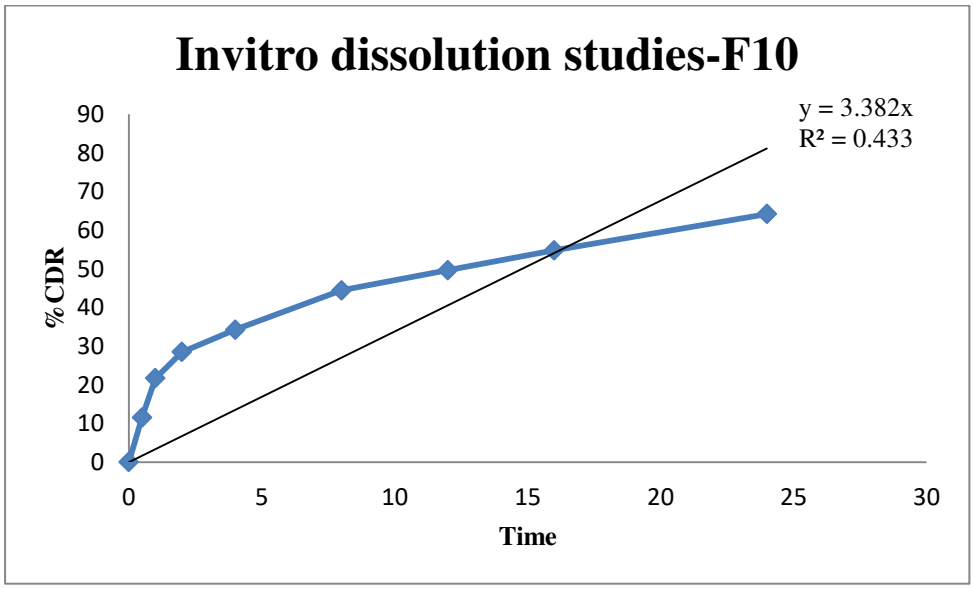


Figure: 16

Curve fitting analysis:

In order to describe the kinetics of the release process of drug in all formulations, various equations were used, such as zero-order rate equation, which describe the system where release rate is independent of the concentration of the dissolved species. The first-order equation describes the release from the systems where dissolution rate is dependent on the concentration of the dissolving species.

Higuchi square root equation describes the release from system where solid drug is dispersed in insoluble matrix, and the rate of drug release is related to the rate of diffusion. The Korsemeyer-peppas equation is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved**.** The data obtained from *in vitro* dissolution studies were fitted to zero-order (figure17-26), first-order (figure27-36), Higuchi (figure37-46) and Korsemeyer–Peppas (figure47-56) equations.

The dissolution data obtained were plotted as Time versus cumulative percent drug released as zero order, Time versus log cumulative percent drug remaining as First order release kinetics, Square root of time versus cumulative percent drug released as Higuchi equation and Log time versus log cumulative percent drug released as per Korsemeyer-Peppas equation.

Invitro Release Profile of Zero Order For Formulations F1 To F10

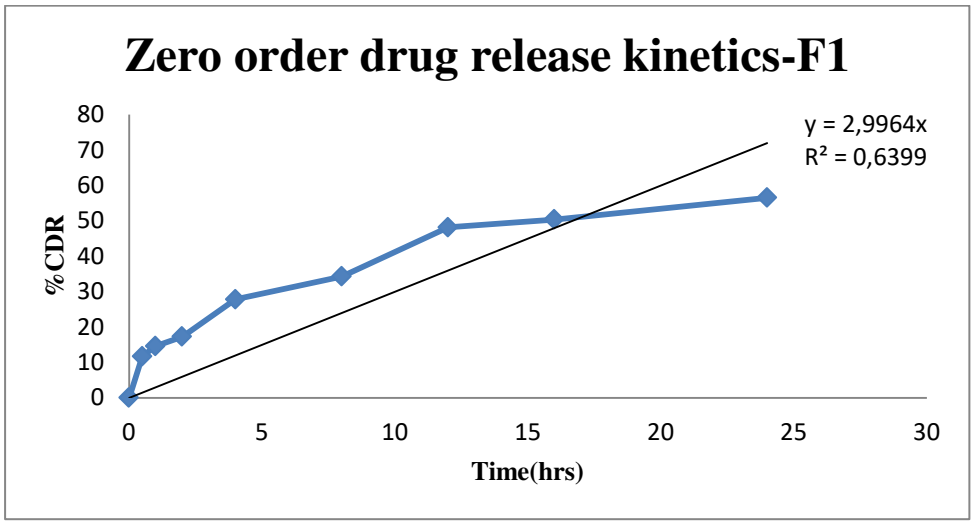


Figure 17: Time vs. Cumulative % drug release for F1 formulation

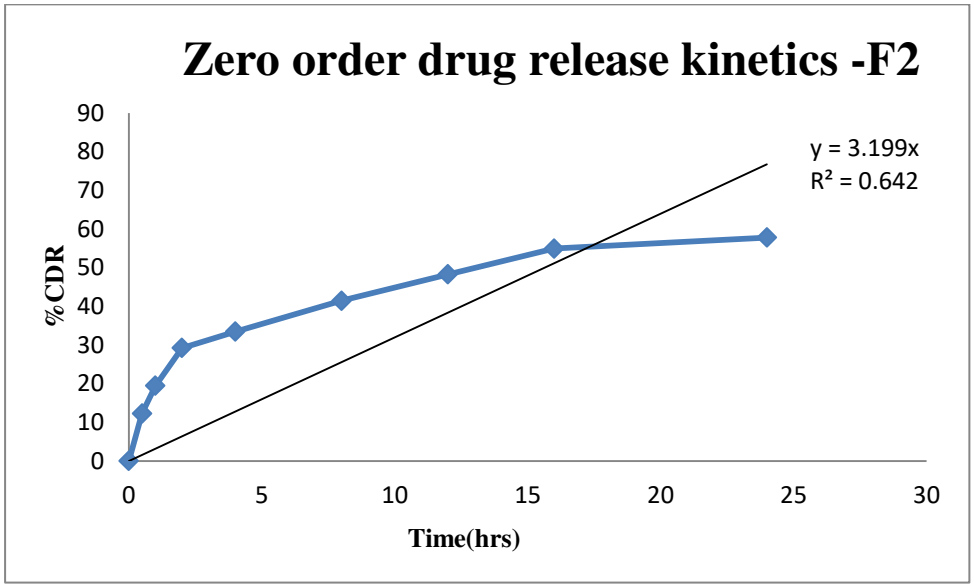


Figure 18: Time vs. Cumulative % drug release for F2 formulation

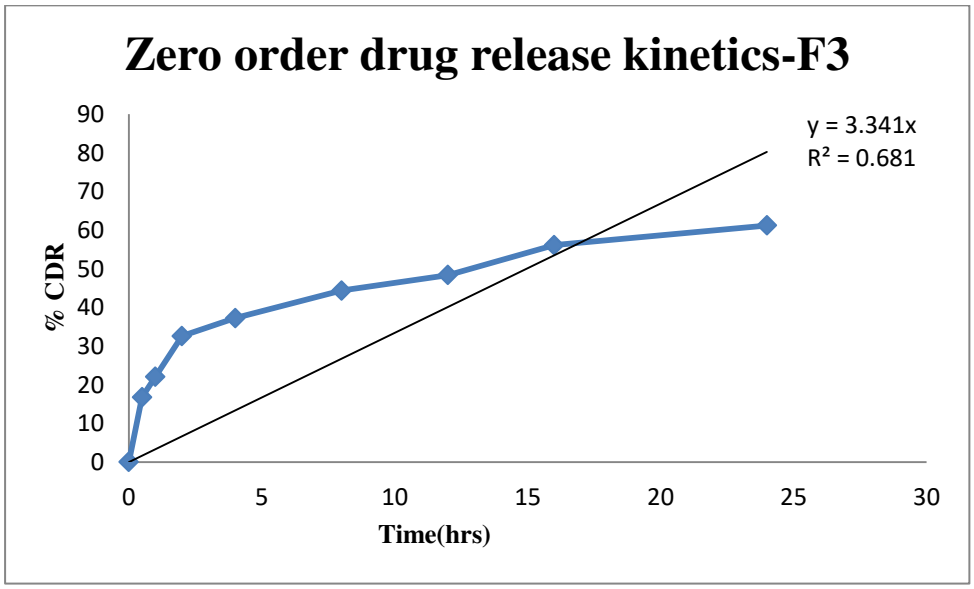


Figure 19: Time vs. Cumulative % drug release for F3 formulation

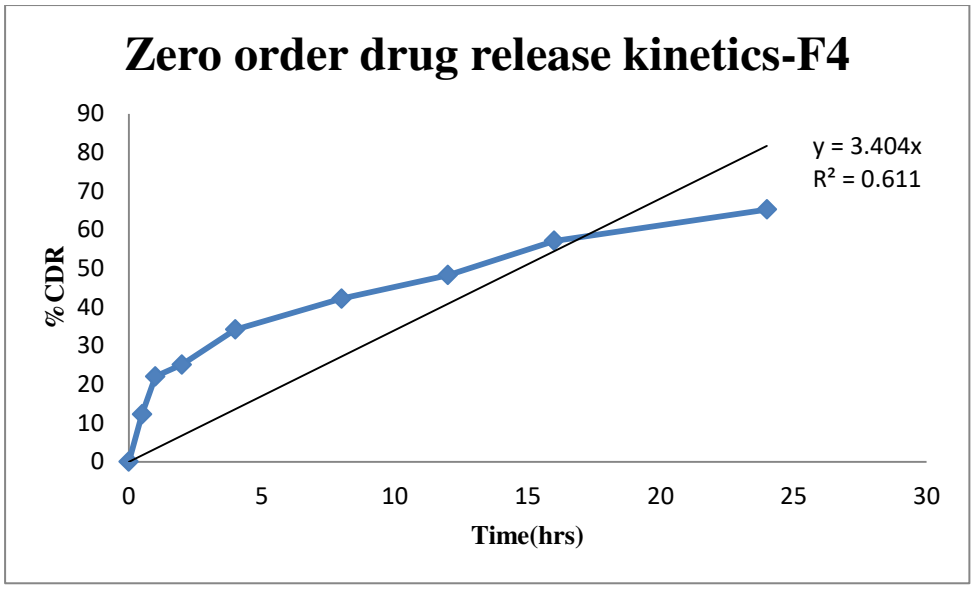


Figure 20: Time vs. Cumulative % drug release for F4 formulation

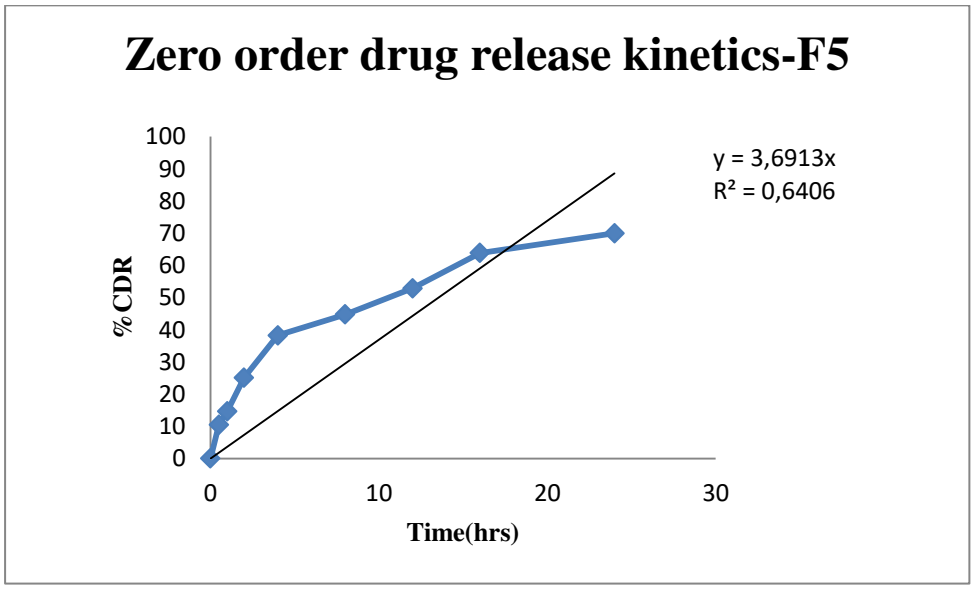


Figure 21: Time vs. Cumulative % drug release for F5 formulation

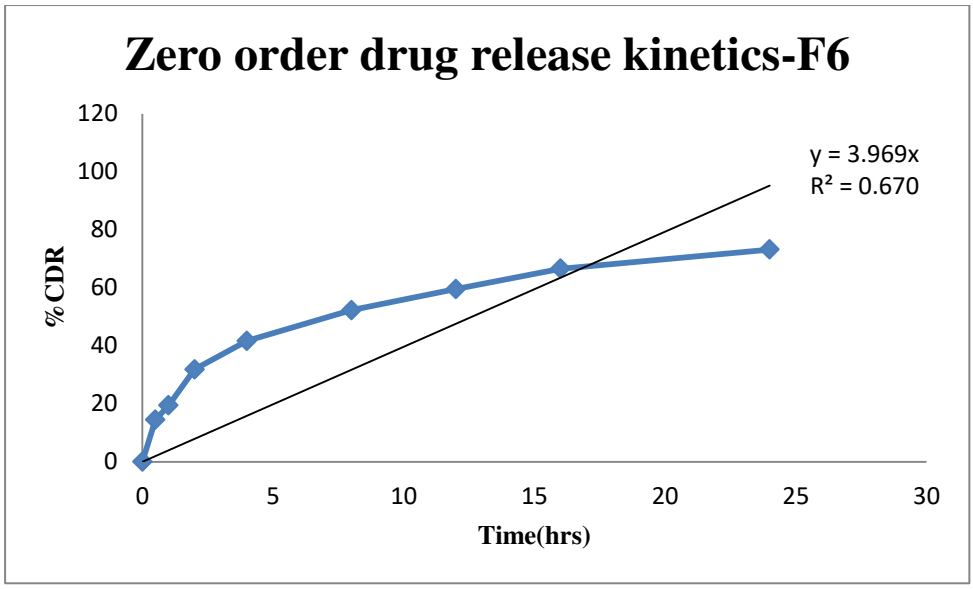


Figure 22: Time vs. Cumulative % drug release for F6 formulation

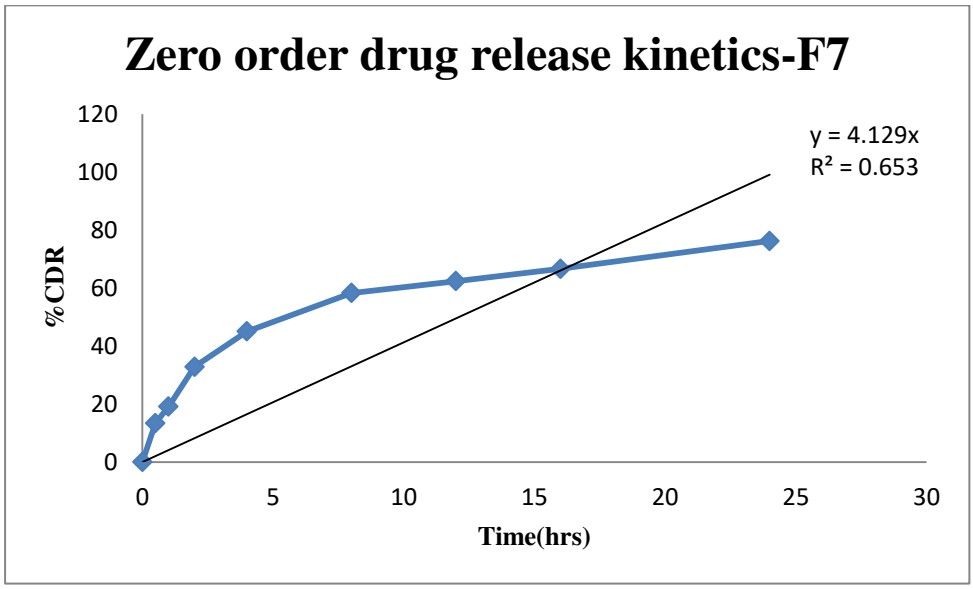


Figure 23: Time vs. Cumulative % drug release for F7 formulation

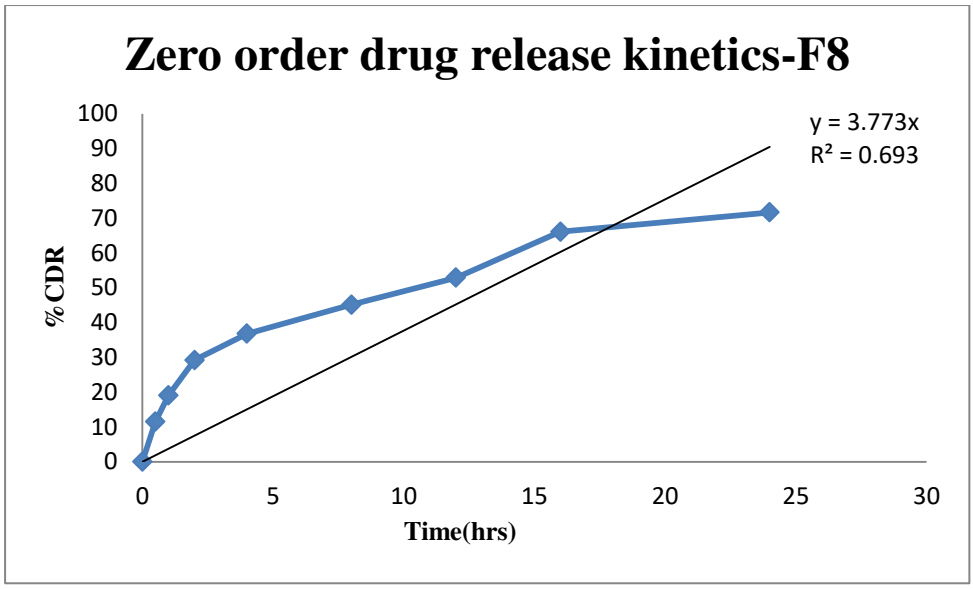


Figure 24: Time vs. Cumulative % drug release for F8 formulation

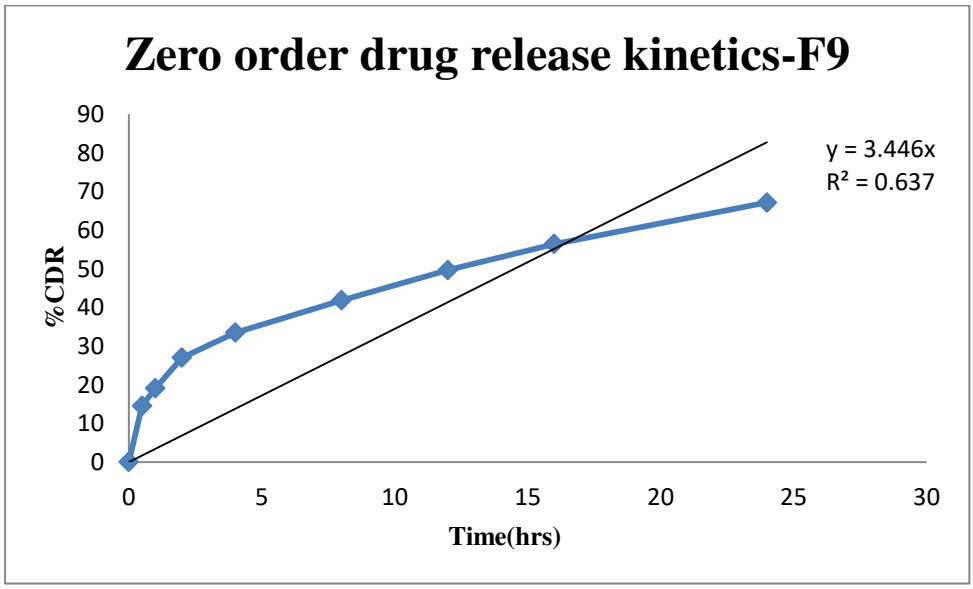


Figure 25: Time vs. Cumulative % drug release for F9 formulation

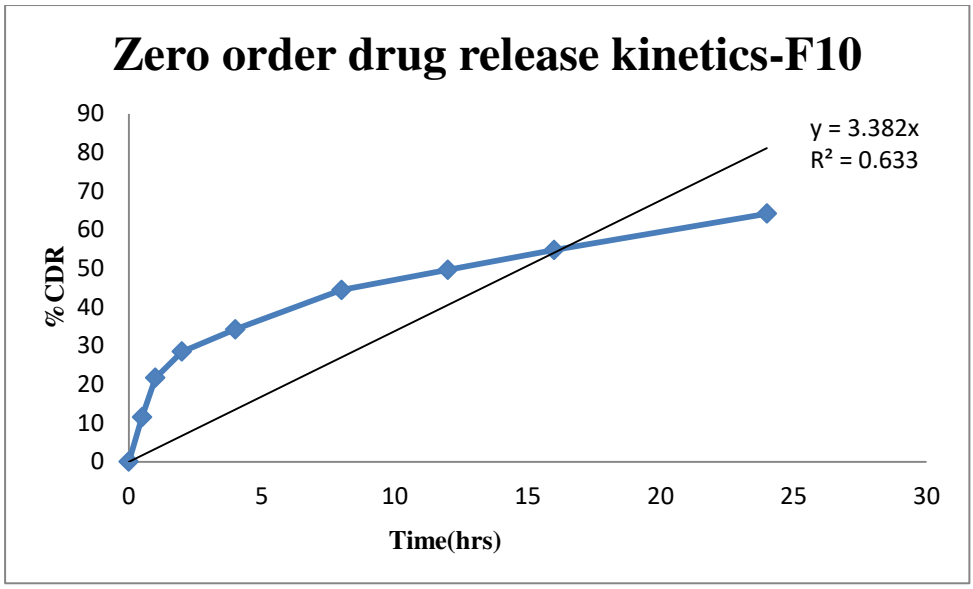


Figure 26: Time vs. Cumulative % drug release for F10 formulation

IN VITRO RELEASE PROFILE OF FIRST ORDER FOR FORMULATION F1 to F10

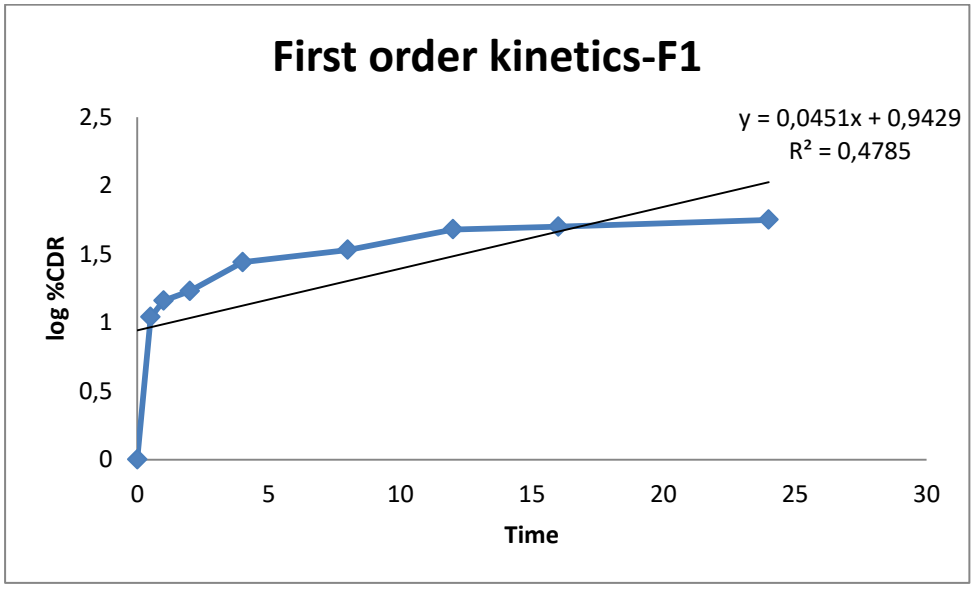


Figure 27: Time vs Cumulative % drug retaining for F1 formulation

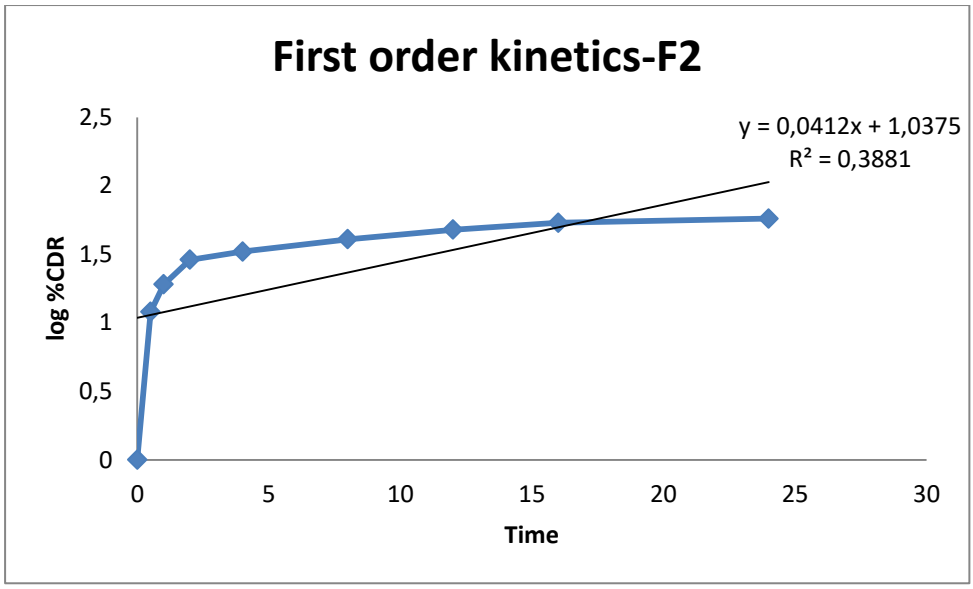


Figure 28: Time vs Cumulative % drug retaining for F2 formulation

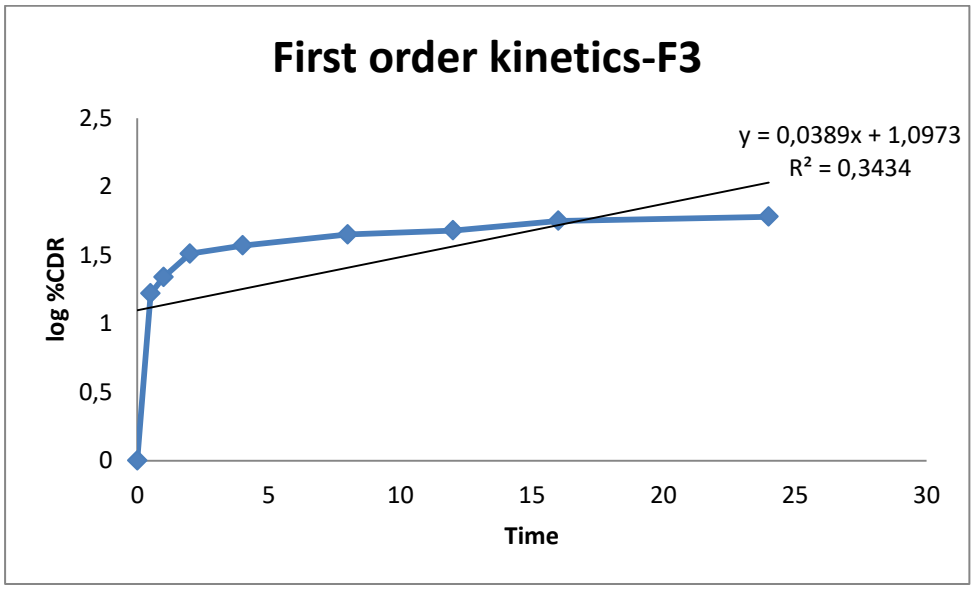


Figure 29: Time vs Cumulative % drug retaining for F3 formulation

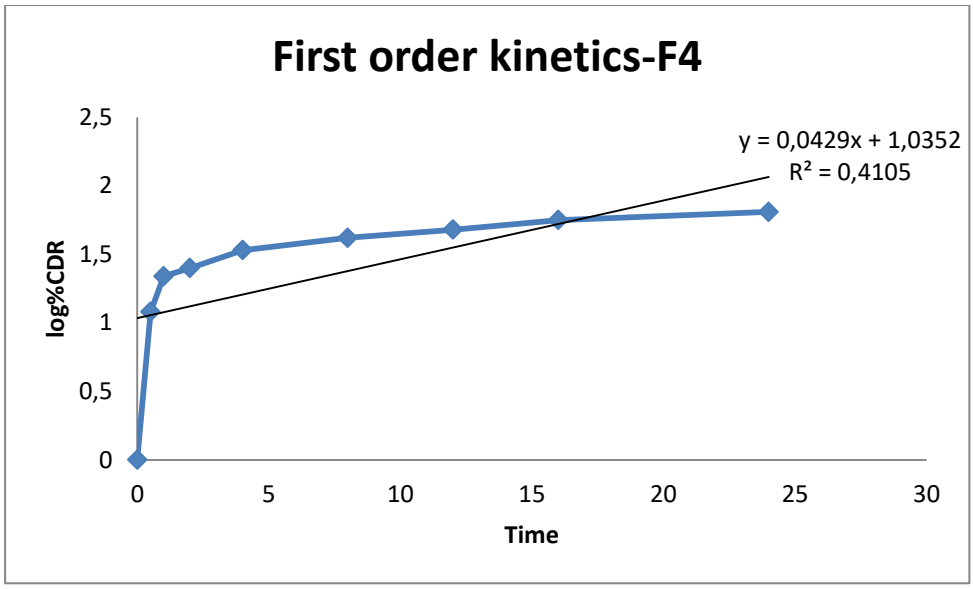


Figure 30: Time vs Cumulative % drug retaining for F4 formulation

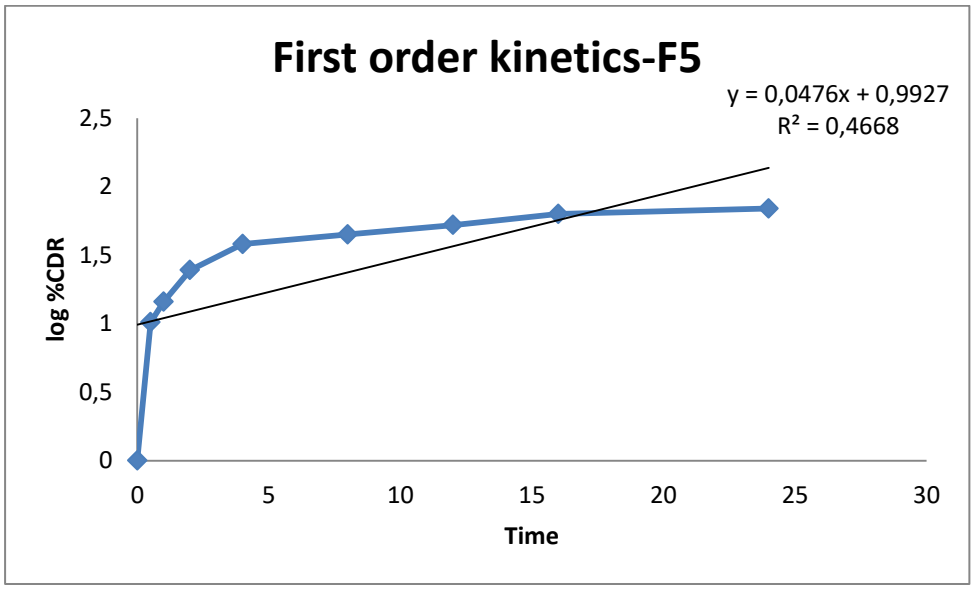


Figure 31:Time vs Cumulative % drug retaining for F5 formulation

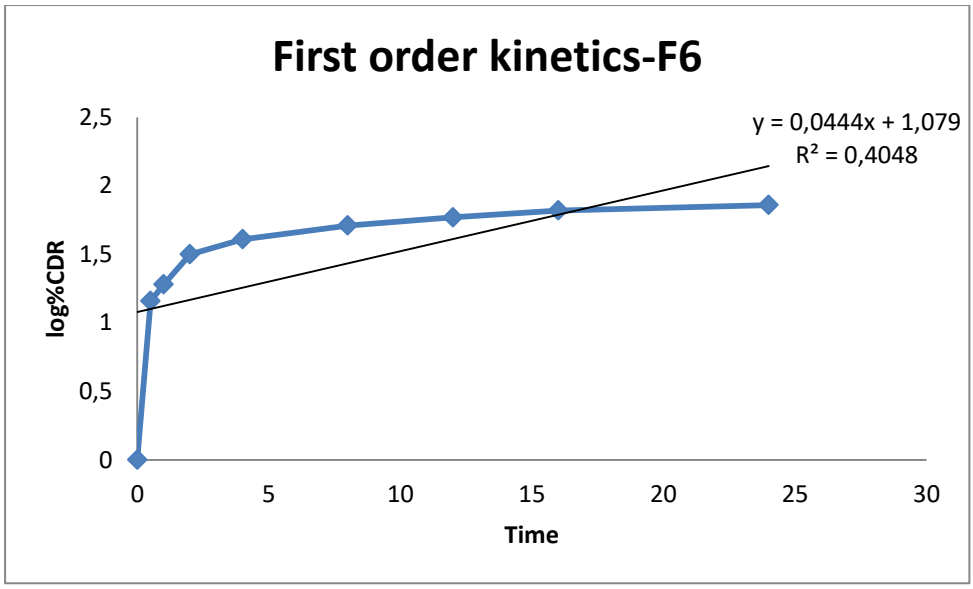


Figure 32: Time vs Cumulative % drug retaining for F6 formulation

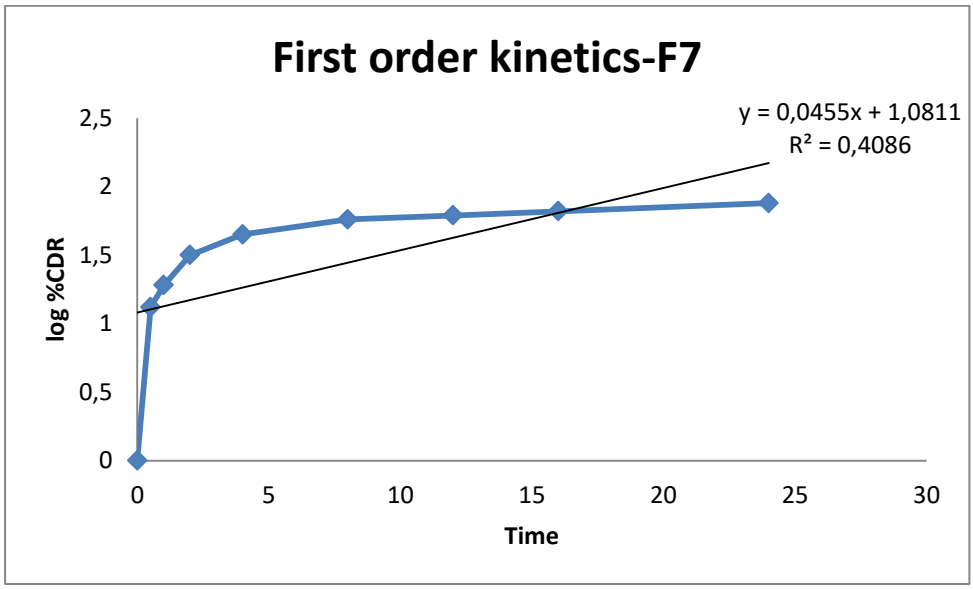


Figure 33: Time vs Cumulative % drug retaining for F7 formulation

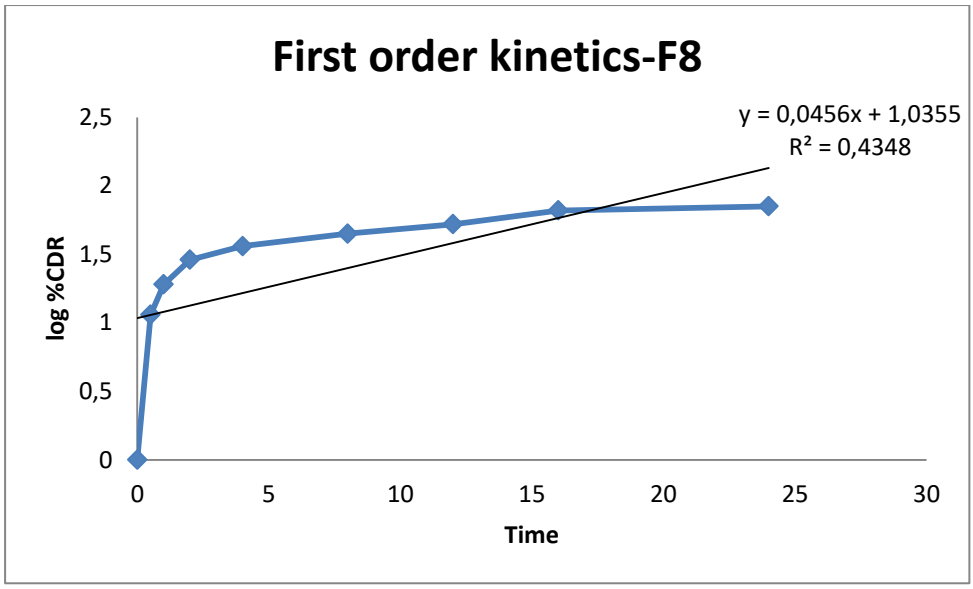


Figure 34: Time vs Cumulative % drug retaining for F8 formulation

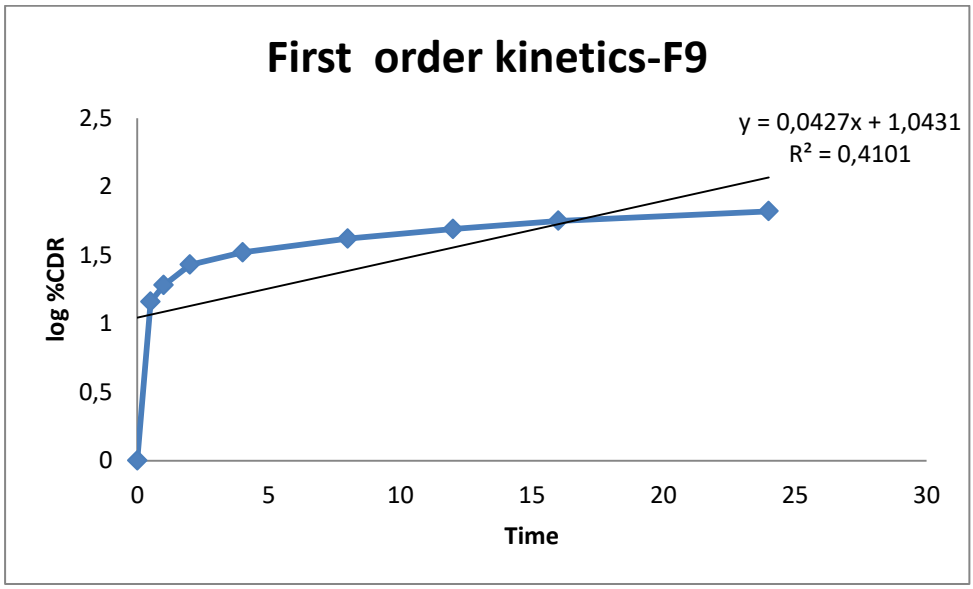


Figure 35: Time vs Cumulative % drug retaining for F9 formulation

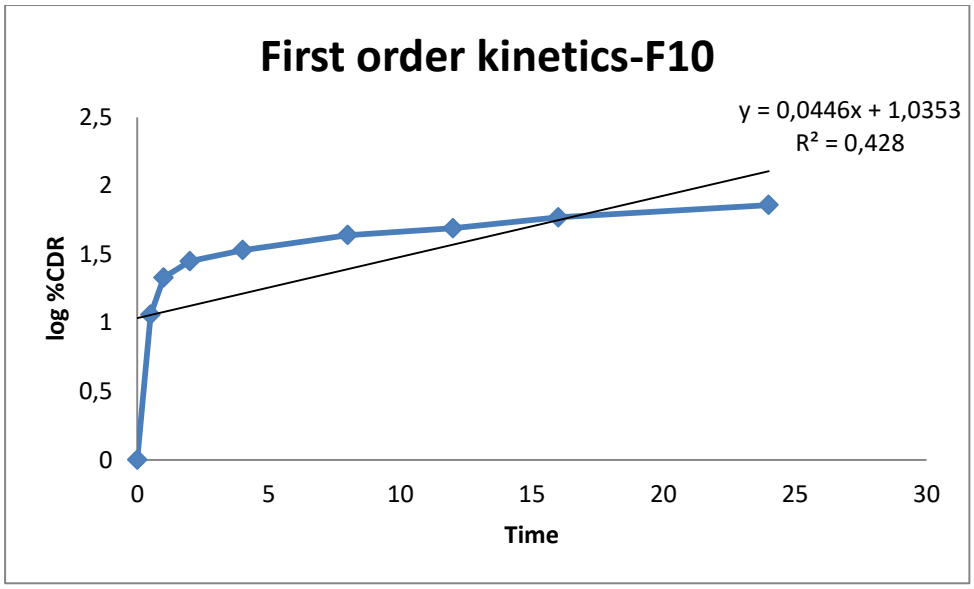


Figure 36: Time vs Cumulative % drug retaining for F10 formulation

In vitro drug release profile of Higuchi model for formulation F1 to F10

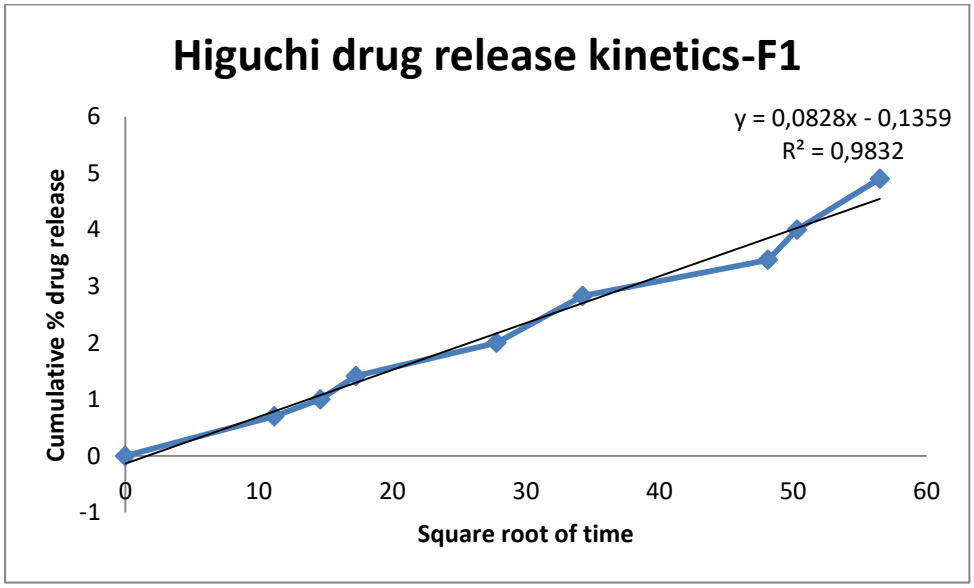


Figure 37: Square root of time vs cumulative % drug release for F1 formulation

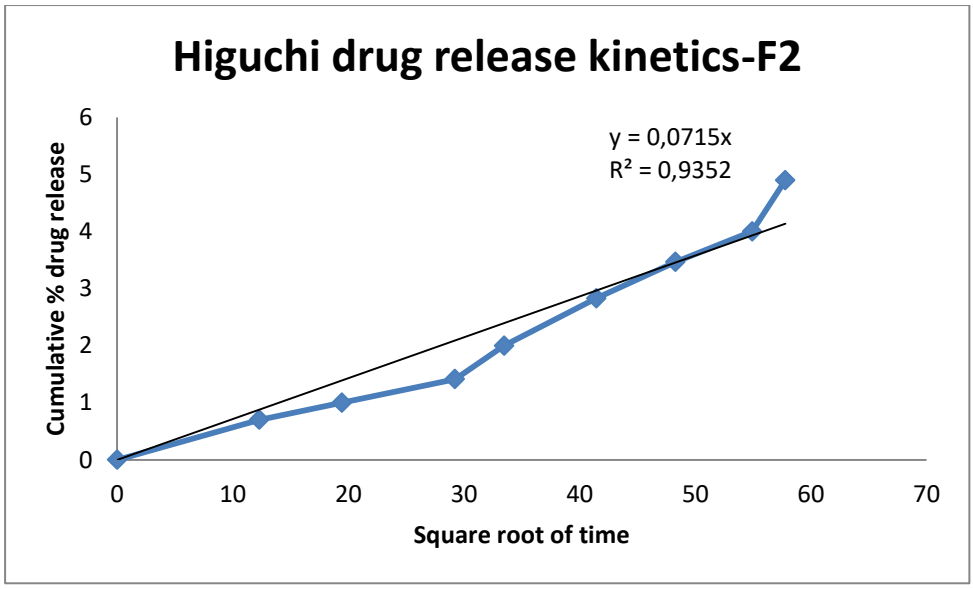


Figure 38: Square root of time vs cumulative % drug release for F2 formulation

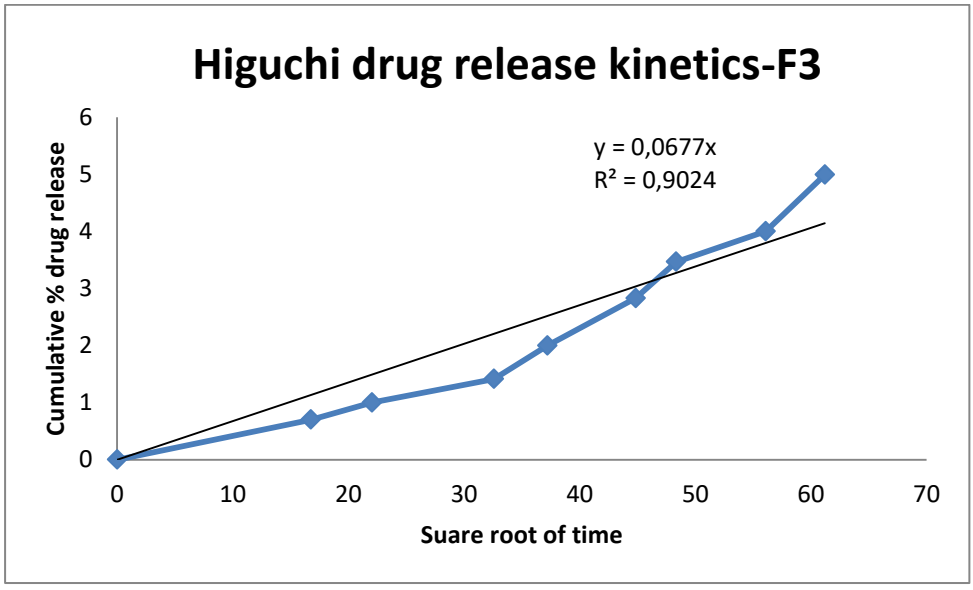


Figure 39: Square root of time vs cumulative % drug release for F3 formulation

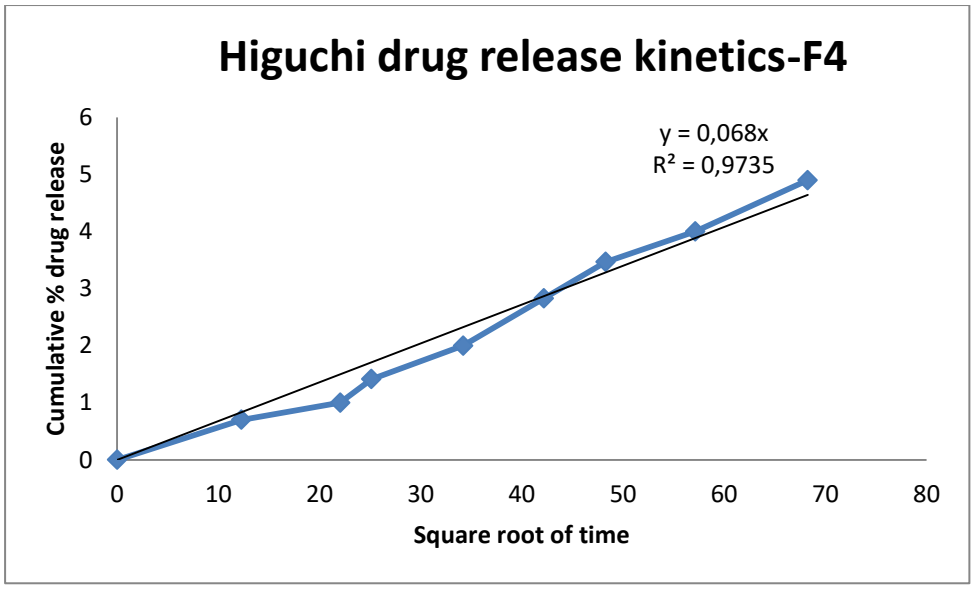


Figure 40: Square root of time vs cumulative % drug release for F4 formulation

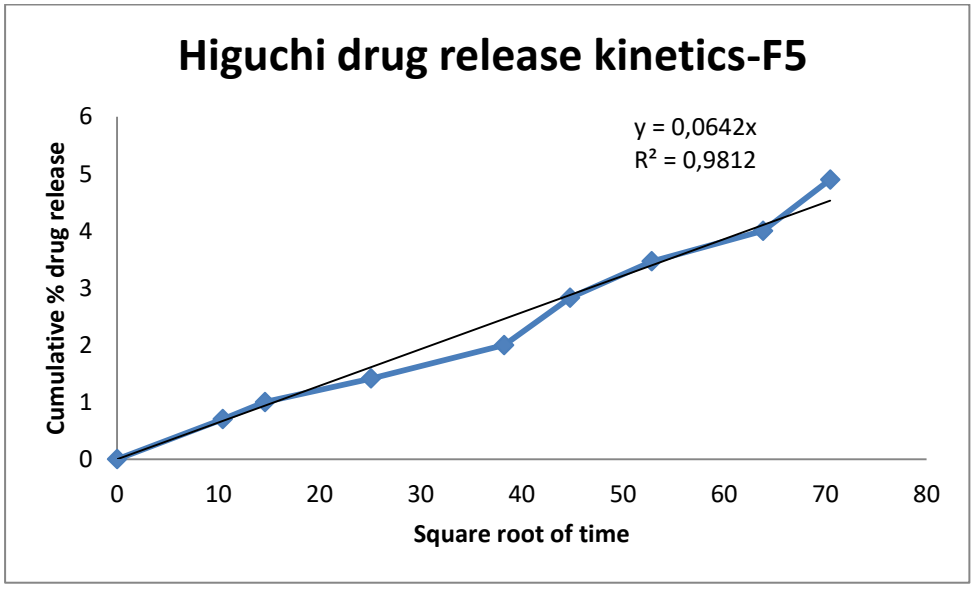


Figure 41: Square root of time vs cumulative % drug release for F5 formulation

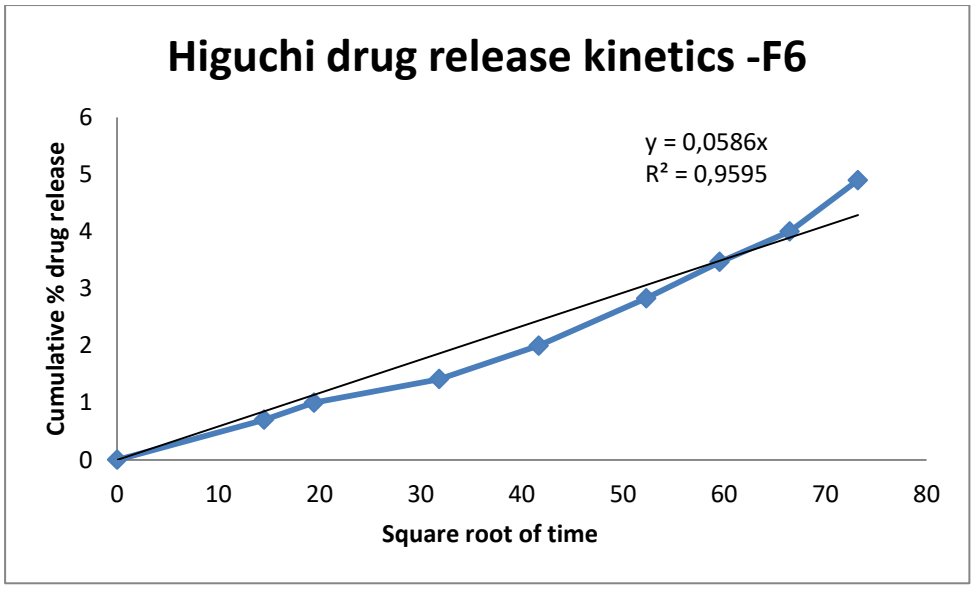


Figure 42: Square root of time vs cumulative % drug release for F6 formulation

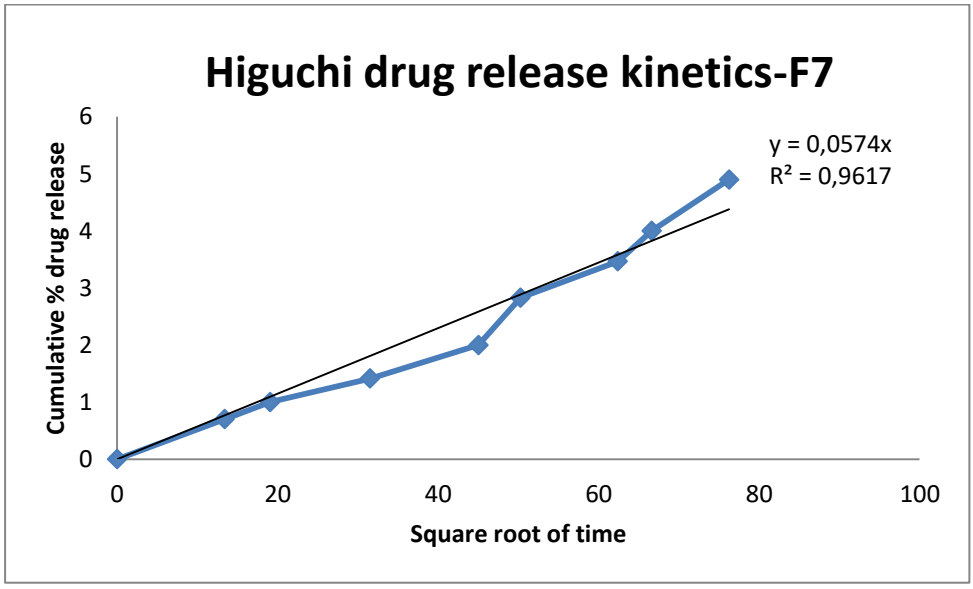


Figure 43: Square root of time vs cumulative % drug release for F7 formulation

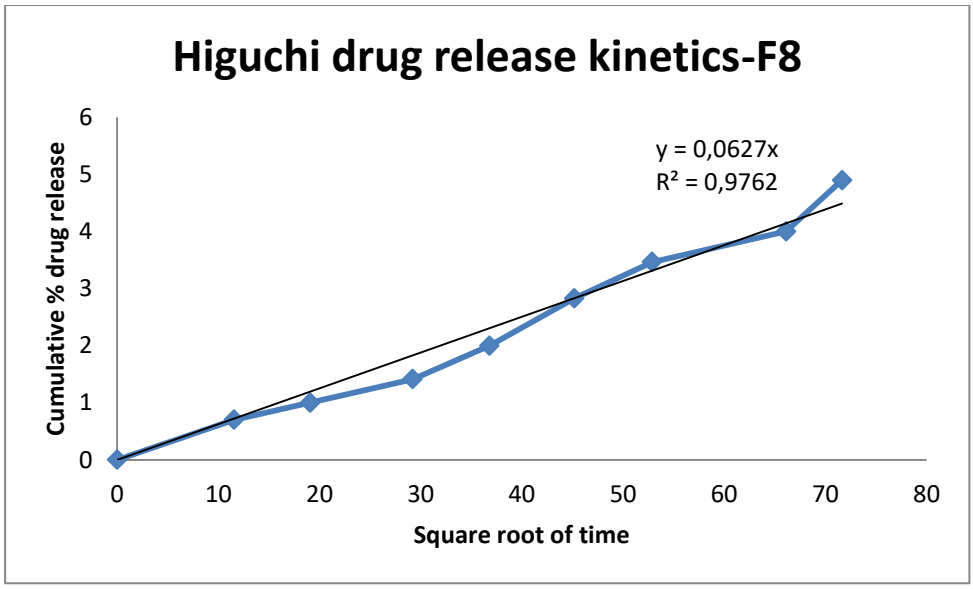


Figure 44: Square root of time vs cumulative % drug release for F8 formulation

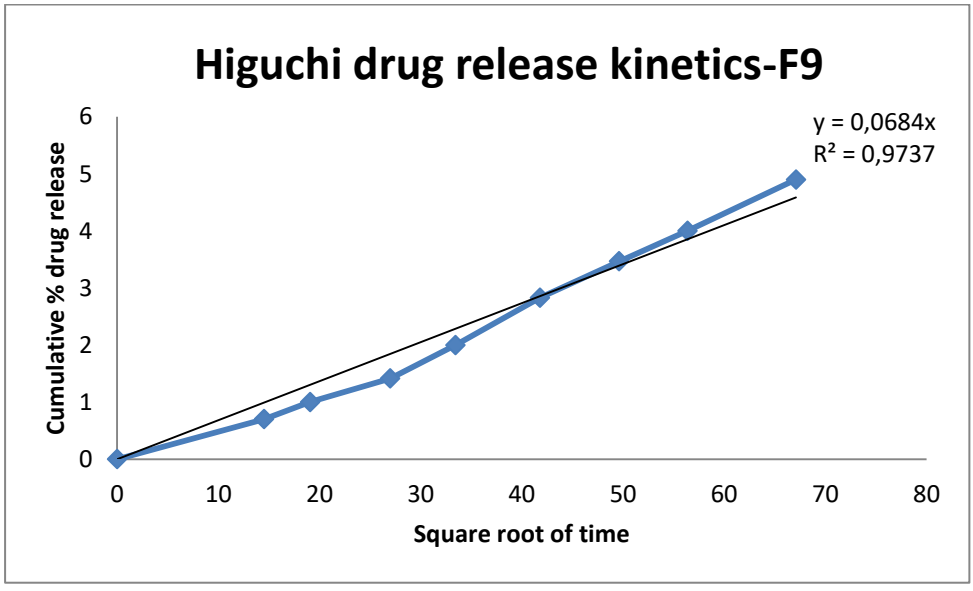


Figure 45: Square root of time vs cumulative % drug release for F9 formulation

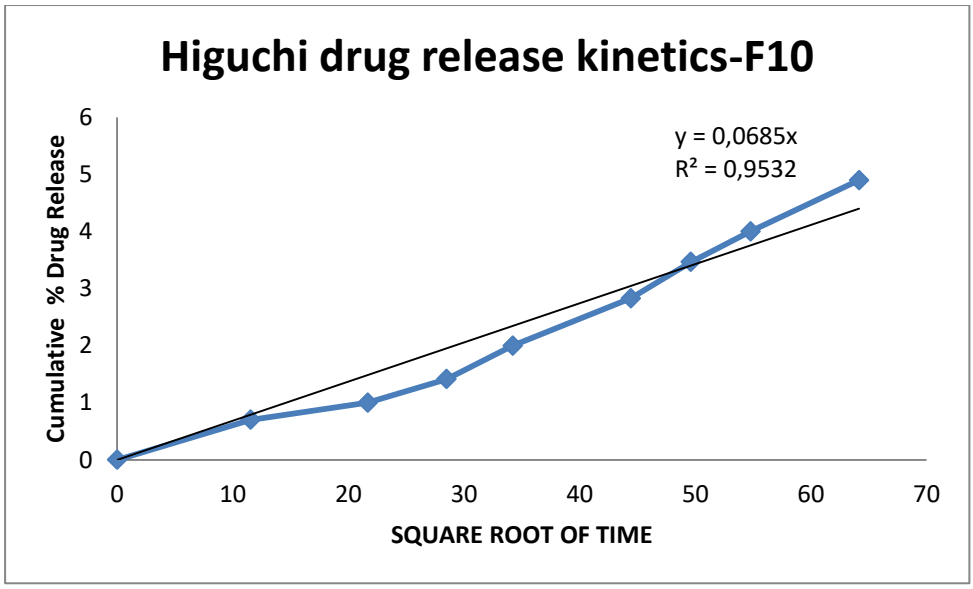


Figure 46: Square root of time vs cumulative % drug release for F10 formulation

In vitro release profile of Korsemeyer's-Peppas model for Formulation F1 to F10

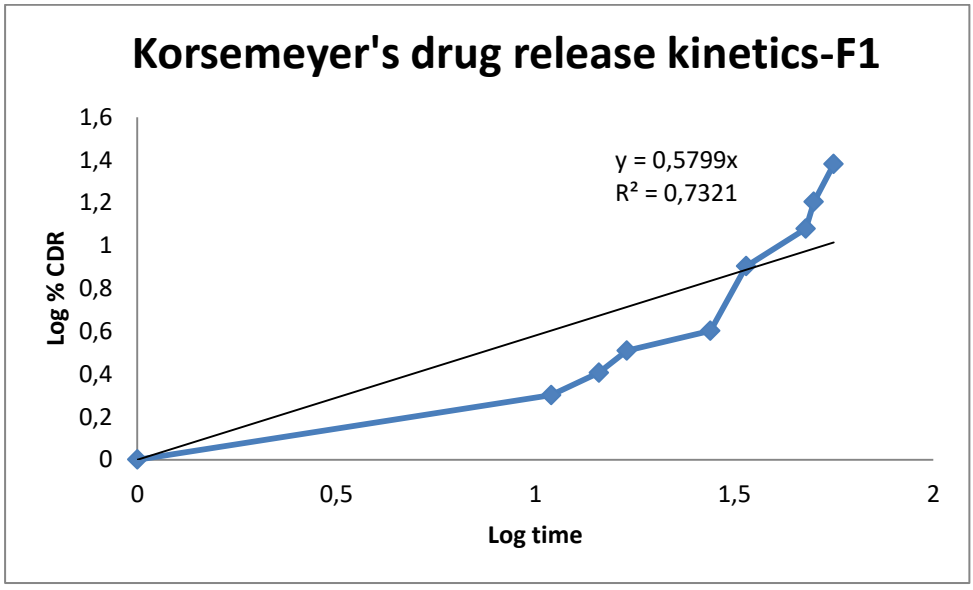


Figure 47: Log time vs log cum % drug release for F1 Formulation

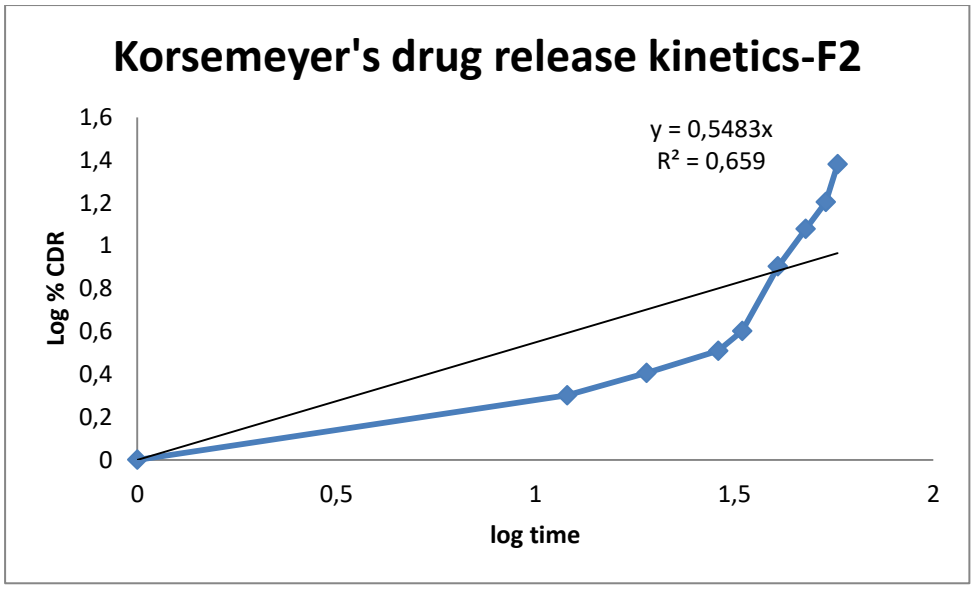


Figure 48: Log time vs log cum % drug release for F2 Formulation

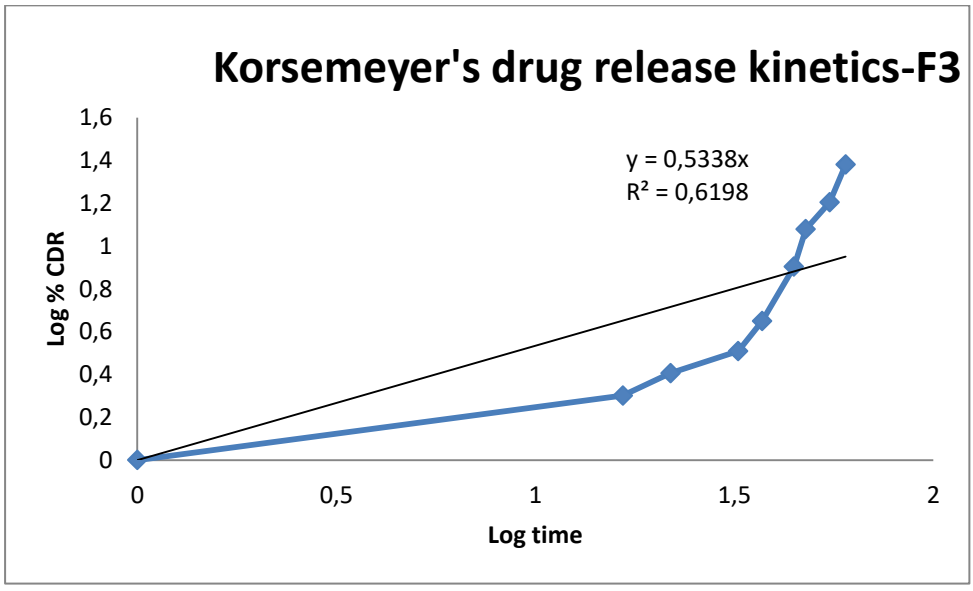


Figure 49: Log time vs log cum % drug release for F3 Formulation

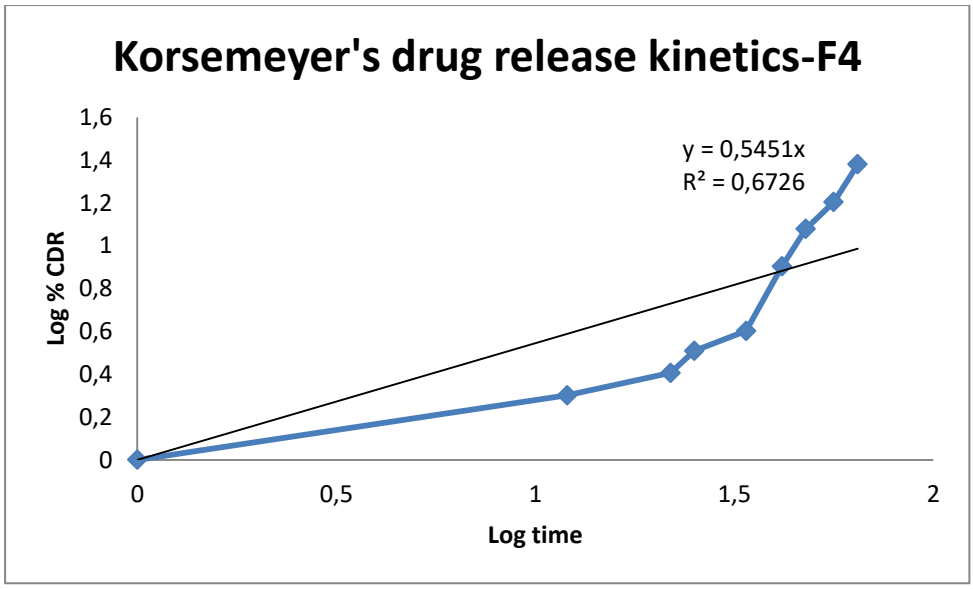


Figure 50: Log time vs log cum % drug release for F4 Formulation

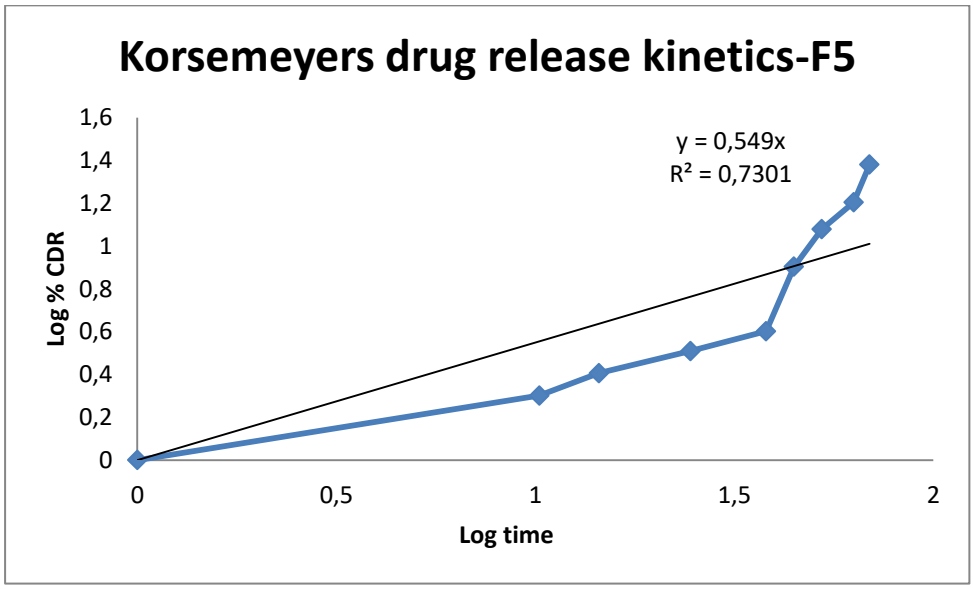


Figure 51: Log time vs log cum % drug release for F5 Formulation

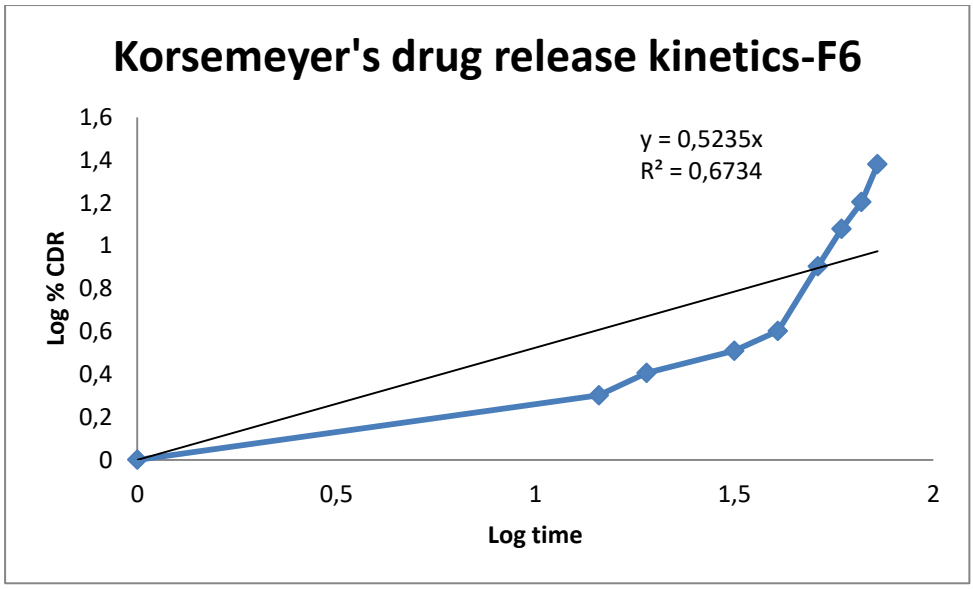


Figure 52: Log time vs log cum % drug release for F6 Formulation

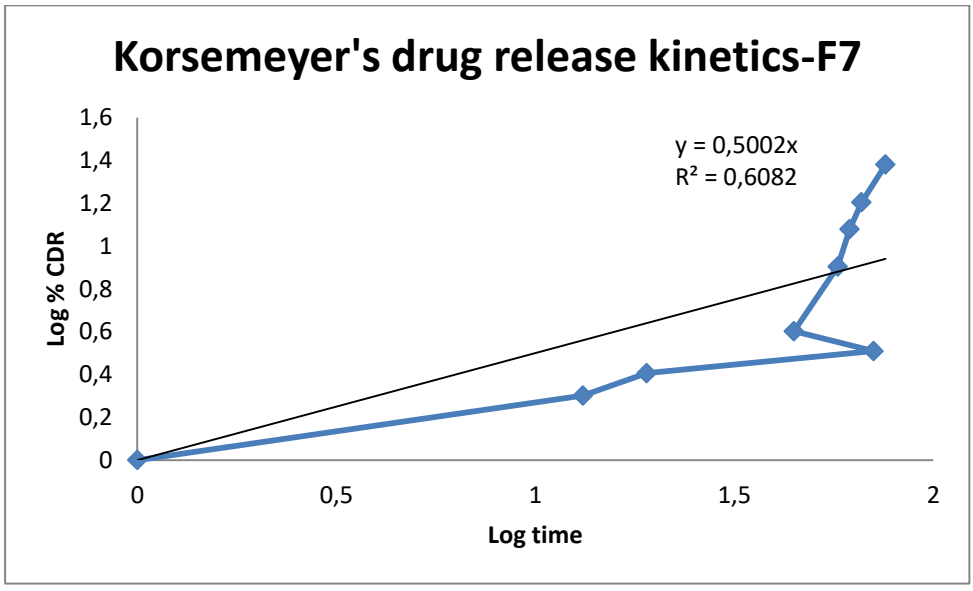


Figure 53: Log time vs log cum % drug release for F7 Formulation

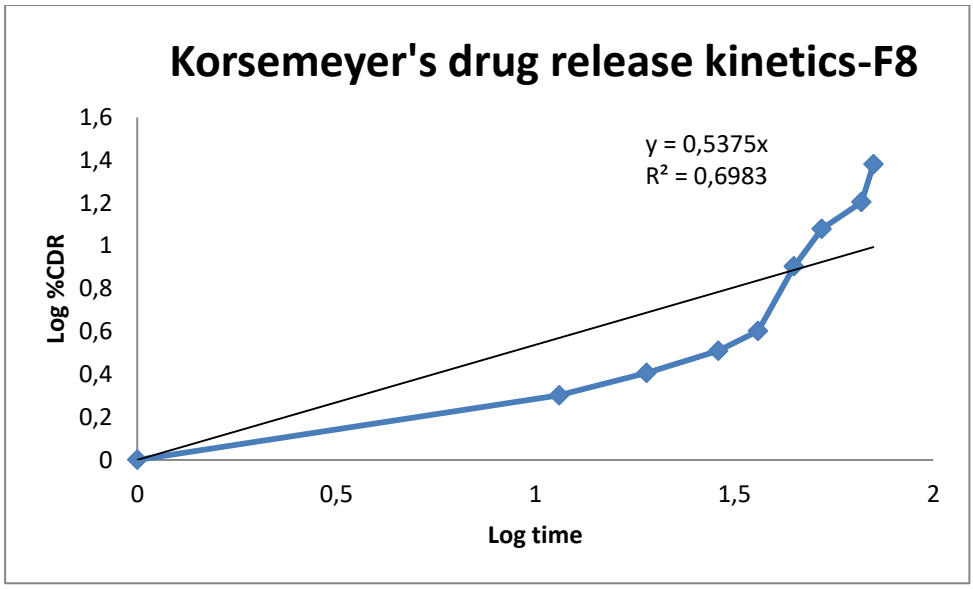


Figure 54: Log time vs log cum % drug release for F8 Formulation

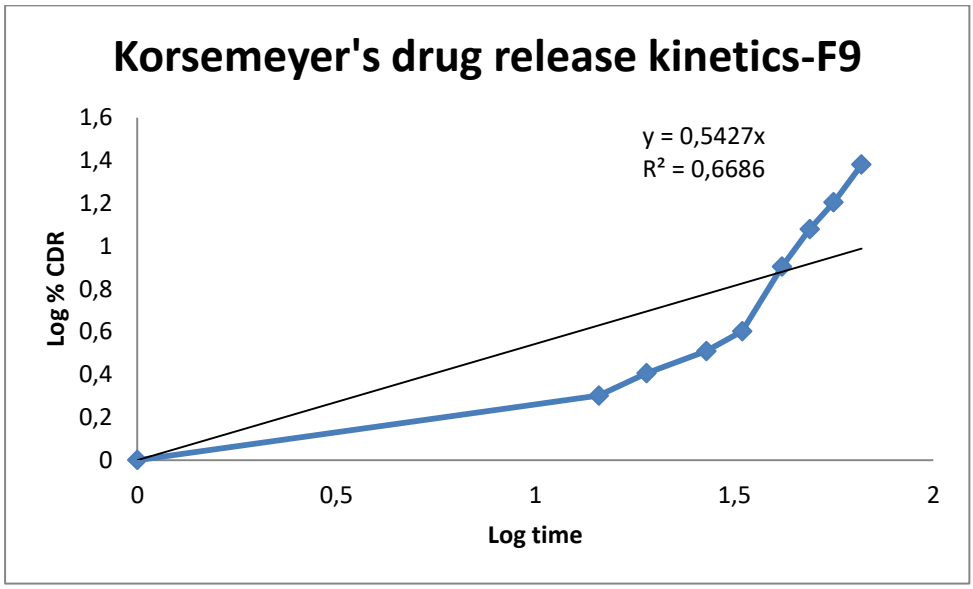


Figure 55: Log time vs log cum % drug release for F9 Formulation

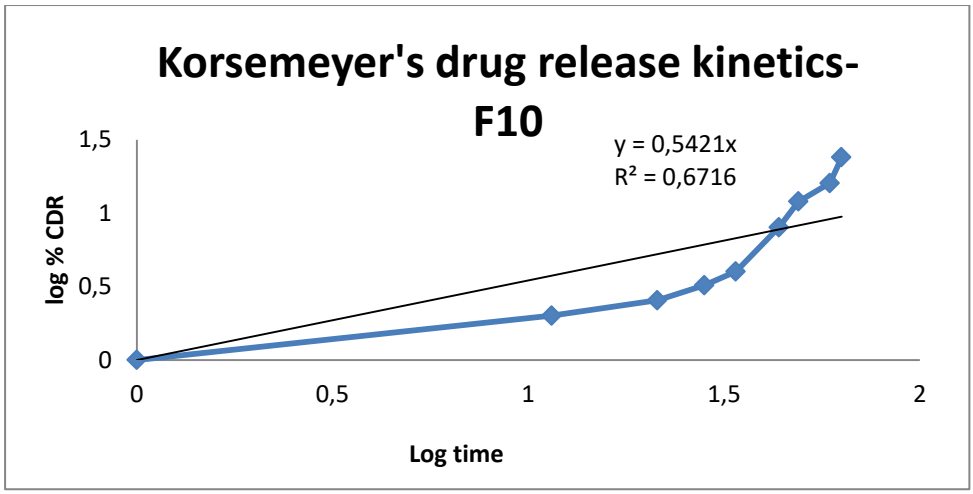


Figure 56: Log time vs log cum % drug release for F10 Formulation

Formulation code	Zero order R^2	First order R^2	Higuchi's R^2	Korsemeyer's N
F1	0.639	0.478	0.983	0.732
F2	0.642	0.388	0.935	0.659
F3	0.681	0.343	0.902	0.619
F4	0.611	0.410	0.973	0.672
F5	0.640	0.466	0.981	0.730
F6	0.670	0.404	0.959	0.673
F7	0.653	0.408	0.961	0.608
F8	0.693	0.434	0.976	0.698
F9	0.637	0.410	0.973	0.668
F10	0.633	0.428	0.953	0.671

Table: 24

DISCUSSION

Microparticles are solid, approximately spherical particles made up of polymeric substances, in which the drug is dispersed throughout the microparticles matrix. It contains an active agent or core material surrounded by a shell or coating of polymers. The shell is a continuous, porous or nonporous, polymeric layer. In biological systems, microparticles are small membrane bound vesicles circulating in the blood derived from cells that are in contact with the bloodstream such as platelets and endothelial cell.

The bonds that link one polymer chain to another are covalent bonds or ionic bonds. Polymer chains are referring to synthetic polymers or natural polymers. Intermediate cross-link densities transform gummy polymers into materials that have elastomeric properties and potentially high strengths. Very high cross-link densities cause materials to become very rigid or glassy. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix finally leads to the cleavage of the hydrolytic bonds.

The cleavage of the bond is also facilitated by the presence of the enzyme in the surroundings. The erosion of the polymer may either surface or it may be bulk leading to the rapid release of water uptake therefore determines release profile of the system and depends on type of the polymer, porosity of the polymer matrix, protein drug loading. Microparticles provide the ability to manipulate the *invitro* action of the drug, pharmacokinetic profile, tissue distribution and cellular interactions of the drug.

PREFORMULATION PARAMETERS:

Compatibility studies:

The drug-excipient interaction study was carried out using FT-IR i.e. by KBr pellet method

Fourier Transform Infrared Spectroscopy:

In the FT-IR drug-excipients interaction study, it was found that Domperidone was compatible with all the excipients used in the formulation. There were no extra peaks observed. Thus the chosen excipients for the formulation were found to be compatible with the active ingredient and have no physical interaction with the active pharmaceutical ingredient.

Determination of λ_{max} of Domperidone:

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. By scanning the drug in U.V spectrophotometer in 200-400 nm range, a sharp peak was observed at 284 nm using methanol as solvent. It was concluded that the drug has λ_{max} of 284nm.

Preparation of standard calibration curve of Domperidone:

From the standard curve of Domperidone it was observed that the drug obeys Beer's law in the range 2-20µg/ml and the equation was generated, Absorbance = 0.021 Concentration + 0.000, was used to calculate the drug content and % CDR of the dosage form.

FORMULATION OF DOMPERIDONE MICROPARTICLES:

Microparticles were prepared ionic-gelation method. Pectin, guar gum and xanthun gum were used as polymers to prepare Microparticles and methanol was used as a solvent. Morphology of Microparticles, %Entrapment efficiency, Drug content, Particle size and *invitro* drug release were selected as dependent variables.

EVALUATION PARAMETERS:

Morphology of Microparticles:

The shape of all formulations was found as smooth and spherical in shape.

Entrapment efficiency:

Highest entrapment efficiency of 80.24 %was obtained with formulation F5. Lowest entrapment efficiency of 23.1% was obtained with formulation F1. For all other formulations (F2 to F10) the entrapment efficiency was found in between minimum and maximum values.

Drug content:

The highest drug content was found to be as 88.83% for F5 formulation and lowest as 40.0% for F1 formulation. For all other formulations (F2 to F10) the drug content was found in between minimum and maximum values.

In vitro drug release:

In first hour of dissolution studies the drug release was observed ranging from 10.58% to 18.42 % for all the formulations. As the Microparticles show the 100% release for 24 hours all the formulations had shown only 76.26% to 54.09% maximum release for 12 hours. F7 formulation showed the sustained release than other formulations.

Curve fitting analysis:

In order to deduce the probable mechanism of drug release from the dosage form, the results of in vitro dssolution studies were fitted to various kinetic equations. When the data was subjected to zero order and first order kinetics model, a linear relationship was observed with high' r2 ' values for zero order model as compared to first order model and it suggested that the formulations followed zero order controlled release.

Higuchis model was applied to the *invitro* release data, linearity was obtained with high r^2 values suggested that the drug release from the Microparticles followed dissolution mechanism.

8.**SUMMARY**

Domperidone is an anti-dopaminergic drug agent that is used orally, rectally or intravenously, in general to suppress nausea and vomiting, as a prokinetic agent and for promoting lactation. It is a specific blocker of dopamine receptors. It speeds gastrointestinal peristalsis, causes prolactin release, and is used as antiemetic and tool in the study of dopaminergic mechanisms.

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In the research work an attempt was made to formulate and evaluate the domperidone Microparticles for sustained effect. The domperidone microparticles were prepared by using ionic-gelation method.

The drug-excipients compatibility studies were carried out by using FT-IR technique. Based on the results, excipients were found to be compatible with Domperidone.

In preformulation study, estimation of Domperidone was carried out by systronics UV spectrophotometer at λ max 284 nm using methanol as solvent, which had a good reproducibility and this method was used in entire study.

Formulations were prepared by using pectin, xanthun gum, guar gum as polymers and methanol is used as a solvent. The Morphology of Microparticles, Drug content, %entrapment efficiency, invitro drug release was evaluated.

Entrapment efficiency ranging from 54.04% to 76.26% was obtained. The shape of Microparticles of all formulation was found as smooth and spherical in shape. In 12 hours the drug release was observed ranging from 79.79% to 54.09%.

In order to deduce the probable mechanism of drug release from the dosage form, the results of *in-vitro* dissolution studies were fitted to various kinetic equations.

When the data was subjected to zero order and first order kinetics model, a linear relationship was observed with high' r^2 ' values for zero order model as compared to first order model and it suggested that the formulations followed zero order controlled release.

Future scope:

- *In vivo* studies can be done by using a suitable animal model
- *In vitro-in vivo* correlation studies can be done.

9.CONCLUSION

The present study was an attempt to optimize and characterize the Domperidone microparticles. The main interest in such a dosage form was made to formulate Domperidone for sustained effect and to increase bioavailability.

Domperidone is an anti-dopaminergic drug agent that is used to suppress nausea and vomiting, as a prokinetic agent and for promoting lactation. It is a specific blocker of dopamine receptors, speeds gastrointestinal peristalsis, causes prolactin release. Domperidone microparticles were prepared by using natural polymers pectin, guar gum, Xanthun Gum by ionic-gelation method by using methanol as solvent.

The drug and excipients compatibility was studied by FT-IR, which shows there is no chemical or physical interaction between drug and excipients.

The results indicate that Domperidone microparticles could be successfully formulated by ionic-gelation method to obtain maximum yield, entrapment efficiency, desired morphology, desired and drug release.

The regression coefficient values for peppas model were found to be high, indicating adequate fitting. Among all the ten formulations, F5 possess the highest entrapment efficiency and F7 possess satisfactory *Invitro* drug release studies for extended period of time. So F5 and F7 were considered to be the best formulations.

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11.ABBREVATIONS

PMMA	:	poly methyl methacrylate
DEAE	:	diethylaminoethyl *cellulose*
NHS	:	N-hydroxysuccinimide
BS3	:	bissulfosuccinimidyl suberate
EDC	:	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
SMCC	:	succinimidyl-4(N-maleimidomethyl)cyclohexane-1 carboxylate
PLGA	:	poly Lactic-co-Glycolic Acid (PLGA)
PLA	:	polylactic acid
PEO	:	polyethylene oxide
DMSO	:	Dimethyl sulfoxide
PBS	:	phosphate Buffered Saline
HPH	:	high pressure homogenization
AFM	:	atomic force microscopy
STM	:	scanning tunneling microscopy
AUC	:	area under curve
DDS	:	drug delivery system
PS	:	particle size
Gm	:	gram

mL	:	milli Liter
mg	:	milli gram
mV	:	milli volts
nm	:	nano meter
cm	:	centimetre
mm	:	millimetre
hr	:	hour
µg/ml	:	micrograms per litre.